15th ADVANCED COURSE OF VACCINOLOGY – 2014

Case study:
How to measure the Impact and Safety of a HUMAN PAPILLOMA VIRUS Vaccine introduced in the national programme of GUATEMALA

Background

The Human Papilloma Vaccine (HPV) has been licensed in the European Union, the United States of America and most recently by many Latin American countries including in Guatemala. The vaccine is available in the private clinics. Some resource rich countries have already included the vaccine in their national vaccination programmes including Australia, Canada, France, the Netherlands, and the United States, and few in Latin America: Panama, Mexico and Peru.

The Ministry of Health (MoH) of Guatemala has called upon a meeting of experts to join the national committee on immunization practices (CONAPI) to advice the MoH how to design and implement the measurement of effectiveness and safety of this new vaccine. The matter is quite urgent since the Vice-President of the country has decided and convinced the Minister of Finance that this vaccine is a priority, and they allocated funds for the purchase of 2 million doses for adolescents 11 to 12 years of age. The Vice-President had a special interest in the vaccine given that her two daughters are now 11 and 9, and she read about the importance of HPV vaccination, and that in Guatemala cervical cancer is the #1 cause of mortality from cancer in women of reproductive age. She is also looking to run for the Presidency in 2016 and she will like to show his achievements for the health of the population.

The MoH is specifically interested in the opinion of this group of experts on the impact of HPV vaccine, but the expert group is expected to give advice on the safety and acceptability of the introduction of the HPV vaccine in the light of the other possibly competing programs like Pap-smear and the acetic acid program provided at health centers.

Task

In preparation for the actual national decision making process and to alert the Ministry of Health (MoH) on the needs of the MoH after inclusion of HPV into the national programme, the group of experts and CONAPI has been called upon for a 1 hour 45 minutes meeting of preliminary discussions. By the end of the session your group will have to come up with a short summary of your views on HPV implementation to be presented.

The Minister of Finances who is a busy man, expects to hear from the group in a 2 minutes briefing:

- Should there be a program to measure the impact (effectiveness) and safety of HPV vaccine to be implemented into the national program of the country?
- What is the strategy, cost, acceptability and potential risks of the program?

Country specific information

Guatemala is a developing country in Central America, south of Mexico. It has a population of 14.8 million. Annually 360 000 children are born. The country has an overall GDP of US$ 5,200. The infant mortality rate is 30 / 1000 live births and 53% of the population live in poverty

Presently the national vaccination programme contains the following antigens for all children: BCG, DTPw-HepB/Hib, OPV, Rotavirus, PCV13 and MMR. All the vaccines used in the national programme are free of charge to the recipients. Vaccines are bought from PAHO's revolving fund. Vaccines are given by public heath nurses at well baby clinics. Immunization coverage of childhood vaccines has been > 85 % for all antigens including MMR.

HPV vaccine was licensed in Guatemala already in 2008. The price is approximately USD 100 / dose in the private market. Free pap screening is available, but its coverage is not very high. There is a national cancer registry, but it is not very well resourced, and data on cervical cancer is not up to date (See data provided)

The MoH, before the decision by the Vice-President to introduce HPV, had just recently introduced Pneumococcal vaccine based on the special surveillance on laboratory confirmed notifications to the national infectious disease registry, the annual incidence rate of Pneumococcal infections being 14 / 100 000 among those less than 5 years, and 30 / 100 000 among those less than 2 years of age, and 50 / 100 000 among those less than 1 years of age.

Composition of the National Commission on Immunizations (CONAPI)

The National Commission on Immunizations of Guatemala deals with childhood and family immunizations. It consists of the following members

- Chairman (MoH Chief of Immunization Program)
- Secretary (a Pan American Health Organization consultant in immunizations)

Six other members who are:

- Clinical pediatrician with extensive experience in clinical trials
- A virologist who is the national rotavirus specialist, and who has a special interest also in HPV
- A clinical epidemiologist with background in infectious disease epidemiology in national and international context
- a public health nurse with special experience in health education and adverse events monitoring
- a clinical microbiologist who heads the national reference center for pneumococcus and Hib
- pharmacist who is in charge of the national vaccine procurement

The MOH has invited the following experts to aid the decision making process of the NABI

- a health economist with experience in primary health care and vaccine cost effectiveness studies
- the chairman of the Pediatric Infectious Disease Society of Guatemala, who has been involved with the several HPV vaccine clinical trials carried out in the country
- a key representative of the National Children's League, which serves as the major non governmental organization looking after children's rights, major player in the field of creating health messages to parents and in providing continuous professional education of public health nurses in the country

Materials to aid discussion

- lecture notes of the ADVAC 2013 sessions before
- country specific information: HPVprofile GTM
- Papers on HPV program introduction and evaluation

Advice on the group work process

Choose the chairman. Choose the rapporteur. Give each member of the group a role of the different participants at the meeting, and debate the different policy options using your knowledge of the vaccines and the diseases of interest as well as the background information provided during the lectures at this course and the literature above. The facilitators of the group will try to provide you with more data should you need it.

- The meeting should last no longer than 1 hour 10 minutes, after which the MOH has arranged the chairman of the expert group to give a preliminary summary of their advice to the Ministry of Finances who presently is drafting the 5-year financial plan of the country.

Evaluating Human Papillomavirus Vaccination Programs

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Human papillomavirus (HPV) has been implicated as the primary etiologic agent of cervical cancer. Potential vaccines against high-risk HPV types are in clinical trials. We evaluated vaccination programs with a vaccine against HPV-16 and HPV-18. We developed disease transmission models that estimated HPV prevalence and infection rates for the population overall, by age group, by level of sexual activity within each age group, and by sex. Data were based on clinical trials and published and unpublished sources. An HPV-16/18 vaccine for 12-year-old girls would reduce cohort cervical cancer cases by 61.8%, with a cost-effectiveness ratio of $14,583 per quality-adjusted life year (QALY). Including male participants in a vaccine rollout would further reduce cervical cancer cases by 2.2% at an incremental cost-effectiveness ratio of $442,039/QALY compared to female-only vaccination. Vaccination against HPV-16 and HPV-18 can be cost-effective, although including male participants in a vaccination program is generally not cost-effective, compared to female-only vaccination.

With 370,000 cases per year and a death rate of approximately 50%, cervical cancer is the third most common malignancy in women worldwide (1,2). Epidemiologic and laboratory evidence has implicated certain types of human papillomavirus (HPV) as the etiologic agents of cervical cancer (3,4). On the basis of this evidence, effort is under way to develop an HPV vaccine that targets these oncogenic HPV types (5).

Clinical trials of preliminary vaccines in humans began in the late 1990s (6). Recent data from an ongoing phase II trial (7) look very positive, demonstrating that an HPV-16 vaccine can prevent HPV infection and precancerous lesions in vaccinated women. These data provide hope that an HPV vaccine may be a reality within 5 to 10 years. Public health officials will then need to make important decisions regarding who and when to vaccinate and what level of vaccine penetration is necessary to substantially reduce disease prevalence.

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Central to this discussion is the question of whether both sexes should be vaccinated. The general assumption in the literature is that men and boys should be vaccinated (5,6,8,9). Although long-term sequelae of HPV infection for men is on average less serious (particularly for heterosexual men), men act as vectors for infection. Including men and boys in a vaccine program would enhance herd immunity and decrease overall incidence of cervical cancer. In this article, we evaluate the benefit and cost-effectiveness of adopting a vaccination strategy for both sexes, compared with that of adopting a female-only strategy. The incremental cost-effectiveness of a vaccination rollout strategy is calculated by dividing the difference in costs between strategies by the difference in quality-adjusted life expectancy.

Because results of the long-term phase III/IV trial are not available, the efficacy of the HPV vaccine is still unknown. Also, acceptance of an HPV vaccine is likely to vary substantially. Resistance to a vaccine may arise because HPV is a sexually transmitted disease (6,10), although recent studies suggest that an HPV vaccine may be reasonably well accepted (11). We therefore evaluated a wide range of vaccine efficacies and population penetrations to understand what is required for a female-only program to achieve sizeable benefit and to identify the scenarios in which incremental male vaccination makes most sense.

Methods

To capture the effect of a male vaccination program on female HPV infection rates and cervical cancer incidence, we needed to directly model the effect of vaccination on HPV disease transmission dynamics. Therefore, we developed disease-transmission models for HPV-16 and HPV-18, the types associated with most cervical cancer cases and the most likely to be included in HPV vaccines (3,6). For both types, the transmission models estimated HPV prevalence and infection rates for the U.S. population overall, by age group, level of sexual activity, and sex. The models also enabled us to evaluate the effect of

various vaccination programs on prevalence and infection rates.

Long-term equilibrium infection rates by age group, by level of sexual activity, and by sex for each vaccination scenario were determined in the transmission model. These infection rates were then incorporated into a probabilistic decision model. This model estimated the annual incidence of HPV-related precancerous lesions, lifetime cases of invasive cervical cancer, resulting cervical cancer deaths, and total cost of care for a given set of age-specific infection rates. By using the combination of the transmission and decision model, we estimated the effectiveness and cost-effectiveness of alternative vaccine rollout strategies.

Transmission Model Structure

We used Stella software (v7.0.3, High Performance Systems, Hanover, NH) to develop deterministic transmission models for heterosexual transmission of HPV types 16 and 18. Because level of sexual activity and HPV prevalence are highly age-dependent, we divided the population into nine age categories, from age 12 to age 50. We further divided each age category into four subcategories based on level of sexual activity (Table 1). HPV prevalence among their pool of sex partners, infectivity per infected partner, HPV shedding duration, and HPV infection rates were estimated for each age and activity group to develop a natural history transmission model. Vaccine penetration and efficacy were added to evaluate the effect of potential vaccine programs.

In our analysis, persons of both sexes were either HPV infected or uninfected at the beginning of each time period. In each period, uninfected persons could remain uninfected or become infected, on the basis of infection rates by age category (Figure 1). Infection rates were determined by number of sex partners, HPV prevalence among pool of sex partners, and infectivity per infected partner. HPV prevalence among the pool of sex partners was a function of HPV prevalence by age and risk group, and by sexual mixing patterns (preference of partners in different age groups for partners in different sexual classes) between age groups and between high- and low-risk sexual activity groups (Table 1). Details regarding the transmission model can be found in the online Appendix (http://www.cdc.gov/ncidod/EID/vol10no11/04-0222_app.htm).

Transmission Model Data

Sex Partnering

The level of sexual activity and mixing patterns between subgroups can affect the transmission dynamics of a sexually transmitted disease (23,24). Table 1 shows our estimates for these variables, based on a survey of the published literature. On average, the number of new sex partners per year for a person in our cohort increases from onset of sexual activity to age 24 and then decreases through age 50 (12–14). Mixing between sexual activity groups was assumed to be assortive, with a moderate preference to select partners in similar sexual activity groups (22). Mixing between age groups was predominantly older men with younger women (12–14).

Duration of HPV Shedding

Persons infected with HPV in a given period are assumed initially to be actively shedding virus and therefore contagious. In subsequent periods, infections can completely resolve or become dormant. Persons whose infections resolve before precancerous lesions develop are assumed to be at no risk for HPV-related cervical cancers, unless they become reinfected with the virus. Persons for

Table 1. Input variables[a,b]

Age category (y)	New sex partners/y (%) (12–14)								Mixing between age categories (%) (12–14)[c]						Initial HPV prevalence (%) (15–18)[d]				Duration HPV shedding (%) (19–21)[e]	
	Female				Male				Female			Male			HPV 16		HPV 18		Stop shedding	Completely regress
	0	1	2–4	5+	0	1	2–4	5+	<	=	>	<	=	>	Female	Male	Female	Male		
<18	64	30	5	1	57	30	11	1		64	36		90	10	2.6	3.5	0.9	1.2	55	49
18–20	55	26	15	4	50	25	19	6	1	61	38	18	72	11	4.3	5.0	1.8	2.1	55	49
21–23	55	26	15	4	50	25	19	6	3	59	38	32	58	10	4.6	5.0	2.2	2.3	55	49
24–26	76	19	4	1	66	21	12	2	11	51	38	34	56	10	3.0	3.4	1.5	1.7	37	33
27–29	83	12	4	1	71	15	12	2	11	51	38	34	56	10	1.7	2.7	0.8	1.4	37	33
30–34	89	7	4	1	76	10	12	2	10	49	41	38	49	13	1.0	2.1	0.5	1.1	37	7
35–39	90	6	3	0	81	9	9	1	13	50	37	36	49	15	0.7	1.5	0.4	0.8	37	7
40–44	90	6	3	0	81	9	9	1	15	48	37	39	47	15	0.5	1.1	0.3	0.6	37	7
≥45	94	5	1	0	90	6	3	0	15	85		39	62		0.4	0.7	0.2	0.4	37	7

[a]HPV, human papillomavirus.
[b]Mixing between sexual activity categories was assumed to be assortive (22). Relative preference for within-group mixing was estimated by [% of potential partners in group X] / [(% of potential partners in group X) + α(1 – % of potential partners in group X)], where α (the assortment variable) ranged from 0.4 for relatively assortive mixing (base-case value) to –0.4 for relatively disassortive mixing.
[c]For each age group, percentage of partners for persons who are in younger (<), the same (=), or older (>) age groups.
[d]Estimate of the prevaccination natural history of HPV infection.
[e]Probability that within 1 year a person of a given age group will stop shedding HPV and the probability that HPV infection will completely regress.

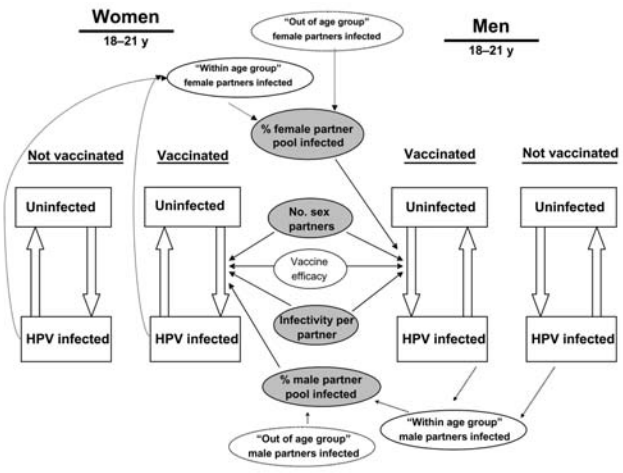

Figure 1. Schematic of the transmission model. The model is divided into nine age categories, with four subcategories per age group (not shown) based on different levels of sexual activity. In each period, uninfected persons can become infected. Infection rates are based on number of sexual partners per year, infectivity per infected partner, and percentage of potential partners who are infected. These variables are age- and risk-group specific. Infection rates for vaccinated persons also depend on the estimated vaccine efficacy. Percentage of potential partners infected includes partners within an age group and potential partners from younger and older age groups. Estimated mixing patterns between age groups differ by sex and age category.

whom the virus has gone into a dormant state can no longer transmit the virus, but they remain at increased risk for precancerous lesions and cancer in the future (Table 1).

Infectivity per Infected Partner

By using our estimates of HPV prevalence among pools of sex partners, numbers of new sex partners, sexual mixing patterns, and duration of HPV shedding, we derived estimates for infectivity per infected partner for persons of both sexes in each age group in the absence of a vaccination program. Infectivity was highest for women and men <18 years, at ≈0.35 infections per infected partner. This number dropped gradually for older age categories (to ≈0.15 infections per infected partner), representing increased resistance to infection and possible changes in sexual activity and practices in these age groups.

HPV Vaccine Characteristics

We assumed that the HPV vaccine would initially be administered by a series of three injections to 12-year-old girls. In our base-case analysis, booster shots would be required for persons in their early 20s. In this scenario, the protective effect of the vaccine lasts for 10 years after the most recent booster. We assumed that the vaccine had 90% efficacy against both HPV-16 and HPV-18 and was given to girls at age 12, with a booster at 22. We assumed 70% of girls were vaccinated, with a vaccine cost of $300 for the initial vaccination (three doses) and $100 for the booster.

Decision Model Structure and Assumptions

In a previous analysis (25), we modeled the overall progression of high-risk oncogenic HPV types to different stages of cervical dysplasia and cancer. In our current analysis, we adapted this model to evaluate the natural history and vaccination scenarios regarding HPV-16 and HPV-18. Estimates regarding Pap screening, lesion treatment, cancer progression and survival, costs, and utilities are based upon our previous analysis (25). Specific progression rate of HPV-16 and HPV-18 to different stages of cervical dysplasia and cancer were estimated from the literature (15,19,20,26,27).

Model Validation

To validate the model, we compared the incidence of cervical cancer cases and deaths predicted by the prevaccination natural history arm of our model with those reported in the Surveillance, Epidemiology, and End Results (SEER) registry (28). Our model's annual rates of cervical cancer cases and deaths matched 2001 SEER estimates within 10%. The predicted age-specific prevalence of HPV infection in our natural history arm also has a shape and peak of similar magnitude to that reported in the literature (15–18).

Results

Base-Case Analysis

Under our base-case scenario, vaccinated girls would experience a 61.8% overall reduction in acquiring cervical cancers over a lifetime. The analysis predicted, given the current U.S. population of 12-year-old girls (approximately 2.0 million), that the number of expected lifetime cases of cervical cancer related to HPV-16 or HPV-18 would drop from 9,147 to 422, a 95.4% reduction. This strategy would add an average of 6.1 quality-adjusted days of life per woman and have a cost-effectiveness ratio of $14,583 per quality-adjusted life-year (QALY) gained compared to the current environment (Table 2).

Vaccinating Men and Boys

If both sexes were vaccinated with an HPV-16/18 vaccine, total cervical cancer cases in that cohort would drop by 63.9%, compared to the number of cases in the scenario before vaccination. The number of cancer cases related to HPV-16 or HPV-18 would decrease from a prevaccination 9,147 to 113, a 98.8% drop from the number in the prevaccination scenario. Expanding the vaccination program to men and boys would add an incremental 0.21 quality-adjusted days of life per woman at a cost-effectiveness

Table 2. Total discounted healthcare costs, total discounted life expectancy in years, and total quality-adjusted discounted lifetime expectancy in years are presented for prevaccination, and for female-only and male + female vaccination scenarios.

Outcome	No vaccination	HPV-16/18 vaccination	
		Female-only[a]	Female + male[b]
Cost, $	40,423	40,667	40,929
Incremental cost, $		244	261
Life expectancy, y	28.7975	28.8112	28.8117
Incremental life expectancy, d		5.0	0.18
Quality-adjusted life expectancy, y	27.7422	27.7590	27.7596
Incremental quality-adjusted life expectancy, d		6.1	0.21
Incremental cost-effectiveness			
$ per life-year		17,802	534,317
$ per quality-adjusted life-year		14,583	442,039
% reduction in lifetime cervical cancer cases		61.8	2.2

[a]Incremental to no vaccination strategy.
[b]Incremental to a female-only vaccination strategy.

ratio of $442,039/QALY compared to the female-only strategy (Table 2).

Vaccine Penetration and Efficacy

Figure 2A shows how varying the vaccine coverage of a female-only HPV-16/18 vaccination program affects the number of lifetime cervical cancer cases. As expected, as vaccine coverage increases, the number of cervical cancer cases decreases. However, based on scenarios that used our transmission model, the relationship is not linear. Because of the benefits of herd immunity, vaccinating even a relatively small portion of the target population leads to substantial decreases in disease prevalence and resulting negative sequelae relative to prevaccination rates. Figure 2A also illustrates the effect of vaccinating both sexes. A combined male-female program always results in lower levels of cohort cervical cancer cases than a female-only program. However, this difference is only large when levels of female vaccine penetration are low.

Figure 2B shows the cost-effectiveness of HPV-16/18 vaccination programs compared to the current environment as coverage varies. The cost-effectiveness of female-only vaccination is attractive at all ranges of vaccine penetration. At lower vaccine penetration levels, including male participants in the vaccination program also becomes cost-effective. For example, at 30% female vaccine penetration, including male participants is reasonably cost-effective at $40,865/QALY compared to vaccinating female participants only. Figures 2C and 2D show similar data for changes in vaccine efficacy.

Vaccination Age

Our analysis assumes that vaccination would focus on children 12 years of age. We considered alternative vaccination strategies that would focus on either infants or persons 18 years of age. Because most women are not sexually active until after age 12, focusing on infants or 12-year-old children leads to approximately the same decrease in lifetime cases of cervical cancer. However, delaying initial vaccination until age 18 leads to only a 54.7% decrease in the number of cancer cases in this cohort. If focusing on the older age group also leads to a decrease in vaccine penetration (60%), then program effectiveness drops further to a 50.9% decrease in lifetime cervical cancer cases in this cohort.

We also considered how the optimal vaccination age was affected if the efficacy of the vaccine waned. If the vaccine efficacy waned over 10 years and no booster was provided, a vaccination program that targeted 18-year-old women would dominate one which targeted 12-year-old girls. In this scenario the cost-effectiveness of also vaccinating 18-year-old men would be economically favorable, with a cost-effectiveness of $57,795/QALY compared to the cost-effectiveness of vaccinating women only. If, however, two booster shots were given at 5-year intervals to maintain the vaccine's efficacy, 12-year-old girls would return to being the optimal vaccination group, but the cost-effectiveness of vaccinating boys would increase to $388,368/QALY.

Effect of Vaccination over Time and Catch-up Vaccination

Under our base-case scenario with an HPV-16/18 vaccine, the first cohort of vaccinated 12-year-old girls would experience a 29.7% decrease in overall cervical cancer cases at a cost-effectiveness of $27,566/QALY, compared to their experience without vaccination. Vaccinating boys would cost $285,776/QALY compared with a female-only program to reduce cervical cancer cases an additional 4.7%. In time, however, lifetime cervical cancer cases would reach a steady-state of ≈62% of prevaccination level. Thus, even the first cohort would experience almost half of the achievable benefit of a long-term vaccination program. Table 3 displays the average reduction in lifetime cervical cancer risk for girls vaccinated at age 12 through a large-scale vaccination program, compared to the

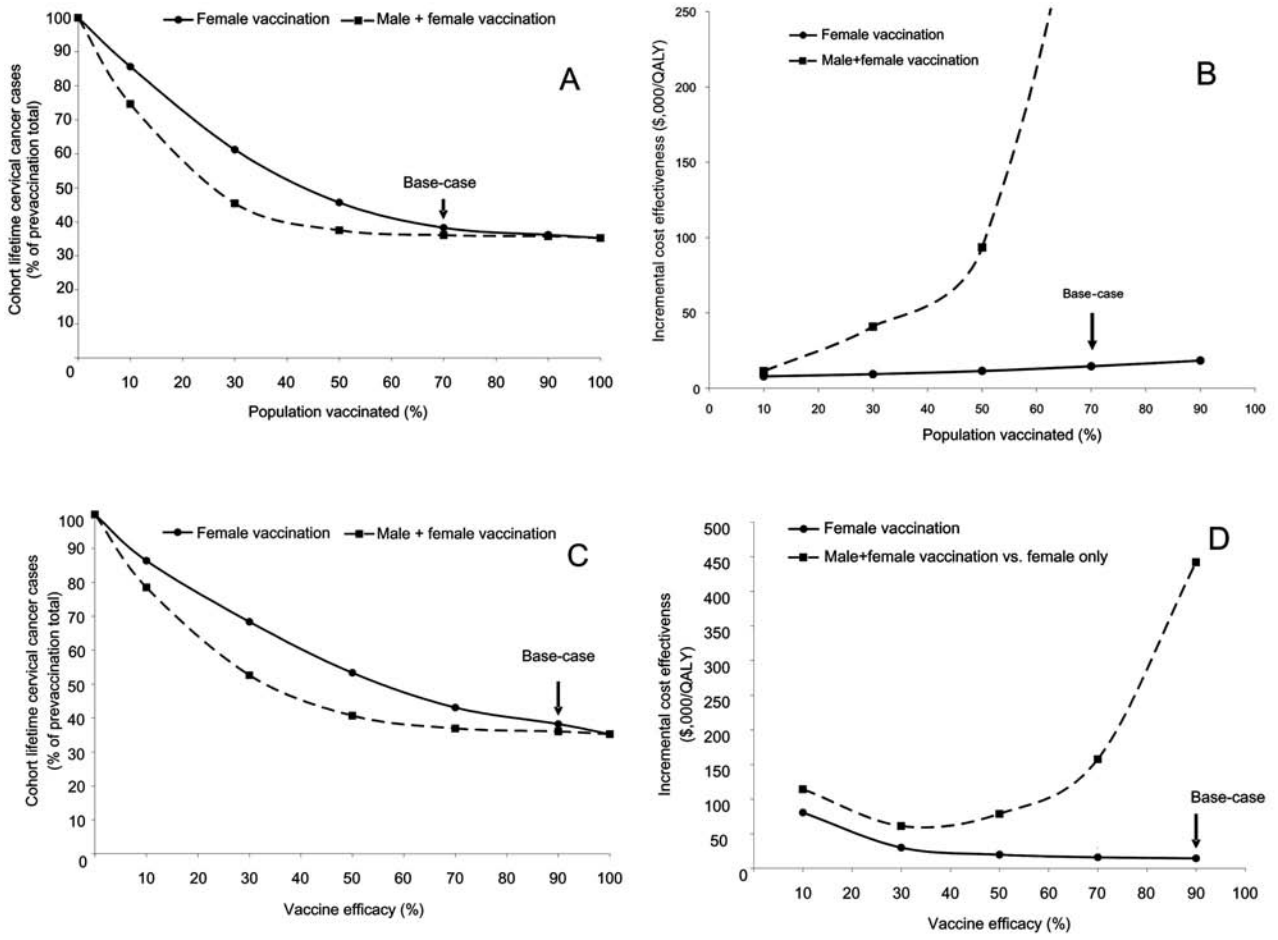

Figure 2. A) Vaccine penetration scenario. Relationship between percentage of the population receiving the vaccine and the number of lifetime cervical cancer cases. The solid line represents a female-only vaccination strategy. The dashed line represents a strategy of vaccinating both sexes. The arrow indicates the base-case scenario of a female-only strategy with 70% penetration. B) Vaccine penetration scenario. Relationship between percentage of the population receiving the vaccine and program cost-effectiveness. The solid line represents the cost-effectiveness ($/quality-adjusted life-year [QALY]) of a female-only vaccination program compared to current practice. The dashed line represents the incremental cost-effectiveness of including male participants in a vaccine program compared to a female-only strategy. The arrow indicates the base-case scenario of a female-only program with 70% penetration. C) Vaccine efficacy scenario. Relationship between vaccine efficacy and the number of cohort lifetime cervical cancer cases. The solid line represents a female-only vaccination strategy. The dashed line represents a strategy of vaccinating both sexes. The arrow indicates the base-case scenario of a female-only strategy assuming 90% vaccine efficacy. D) Vaccine efficacy scenario. Relationship between vaccine efficacy and program cost-effectiveness. The solid line represents the cost-effectiveness ($/QALY) of a female-only vaccination program compared to current practice. The dashed line represents the incremental cost-effectiveness of including male participants in a vaccine program compared to a female-only strategy. The arrow indicates the base-case scenario of a female-only program at 90% vaccine efficacy.

reduction in risk to women ages 24 and 30 who opt for catch-up vaccination once a vaccine becomes available.

Pap Screening Guidelines

Although an HPV-16/18 vaccine would not protect against all oncogenic HPV strains, we wanted to explore whether the vaccine could sufficiently reduce the prevalence of cervical cancer and precancerous lesions to allow for less frequent cervical cancer screening. Our base-case analysis assumes that 71% of women get Pap smears every 2 years (29). Figure 3 presents the cost-effectiveness of moving to more or less frequent screening intervals, in the presence of an established vaccine program.

Sensitivity Analyses

We performed sensitivity analyses on a range of model variables. The female-only vaccination program remained economically attractive under a wide range of variable assumptions. However, the incremental benefit of vaccinating men and boys was sensitive to changes in key variables. Figure 4 shows one-way sensitivity analyses of the cost-effectiveness of incrementally vaccinating male

Table 3. Reduction in lifetime risk of cervical cancer

Cohort	% reduction in lifetime risk of cervical cancer
Full potential of program in 12-year-old girls	64
First cohort of 12-year-old girls vaccinated[a]	46
24-year-old women who receive catch-up vaccination[b]	35
30-year-old women who receive catch-up vaccination[b]	17

[a]This group experiences a lower reduction in cancer cases because many of their sex partners will be drawn from a population pool that has not been vaccinated.
[b]24- or 30-year-old women who opt for catch-up vaccination in the first year that the vaccine becomes available.

participants compared to the cost-effectiveness of female-only vaccination.

Discussion

By using a disease transmission model for the sexual transmission of HPV, we demonstrated that an HPV-16/18 vaccine would be cost-effective and could reduce lifetime cervical cancer cases by 61.8%. Although a universal vaccination program would have the greatest benefit, because of the benefits of herd immunity, a program that achieves even 70% coverage would dramatically reduce cohort lifetime cervical cancer cases.

Although the literature often suggests that men and boys should be included in an HPV vaccination program (5,6,8,9), our results suggest that this strategy may not be the most cost-effective public health strategy. Under our base-case assumptions, including men and boys in a vaccination program would further reduce infections and cancer cases only slightly, with an unattractive cost-effectiveness ratio of $442,039/QALY saved. In addition, the absolute cost of expanding coverage to men and boys is high. Assuming a $300 vaccine, achieving 50%–70% coverage for the current U.S. population of approximately 2.1 million 12-year-old boys would cost >$300 million annually.

In certain scenarios, such as those in which vaccine efficacy wanes rapidly without boosters or overall vaccine coverage is low, vaccinating male participants can have a substantial effect (Figure 4). In a recent article that modeled risk groups but not age groups, Hughes et al. (30) found that for a single-type HPV vaccine with a 10-year mean duration and no booster that was meant for 16-year-olds, a program focusing on girls would have only two thirds of the impact on HPV infection rates as a program focusing on both sexes. Modeling both risk and age groups, we found that the incremental cost-effectiveness ratio of vaccinating boys dropped to $51,646/QALY for a vaccine with rapidly waning efficacy and no booster. Also, if vaccination rates are lower among the most sexually active girls, the female-only vaccination strategy will be less effective. In sensitivity analyses, we demonstrated that vaccinating boys in such a situation would be reasonably cost-effective. For example, if vaccine penetration amongst the highest risk girls reached only 30%, the cost-effectiveness ratio of vaccinating boys drops from $442,039/QALY to $116,413/QALY. Nonetheless, even in this scenario, vaccinating boys is less cost-effective than achieving higher vaccine penetration in girls at high risk (analysis not shown).

We demonstrated that vaccinating women at the onset of sexual activity is cost-effective and will lead to the greatest reduction in cervical cancer incidence. Because we assume that the vaccine will require a booster after 10 years, focusing on 12-year-olds would be more cost-effective than focusing on infants ($27,600/QALY). If a vaccination program focusing on infants were more widely accepted, with initial coverage of 80% versus 70% in the base-case scenario, we would expect only an additional 1.2% decrease in overall lifetime incidence of cervical cancer, and the cost-effectiveness ratio would increase to $28,181/QALY. Focusing on 18-year-olds would limit the efficacy of the vaccine program and is not recommended unless focusing on younger groups is not possible.

We explored the effect of changing cervical cancer screening interval guidelines once a vaccine program was established (Figure 3). Even in a prevaccination environment, researchers found that moving from screening every 2 years to every year is not particularly cost-effective (31). Kulasingam and Myers recently found that Pap testing may be delayed to a later age than currently recommended when an HPV vaccine has been given; although that analysis did not include disease-transmission dynamics and

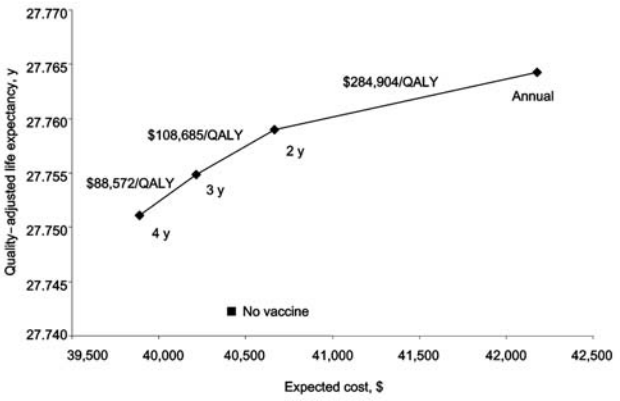

Figure 3. Effect of changing frequency with which vaccinated women receive a Pap test. The diamonds represent Pap testing annually, every 2 years (base case), every 3 years, and every 4 years. The x-axis represents the lifetime expected cost of the vaccination strategy; the y-axis is the quality-adjusted life expectancy in years. The incremental cost-effectiveness of increasing the frequency of Pap testing for vaccinated women is indicated numerically above the cost-effectiveness frontier. QALY, quality-adjusted life-year.

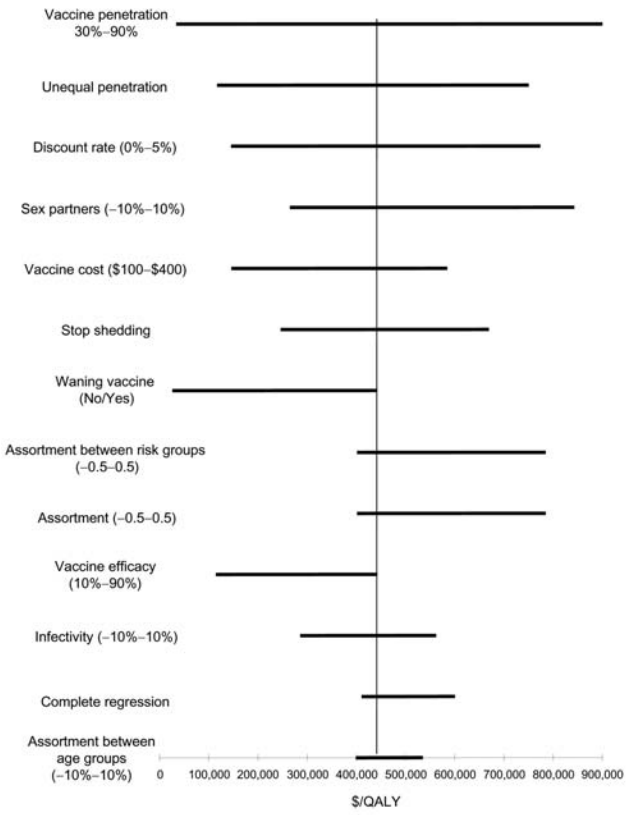

Figure 4. Tornado diagram representing the incremental cost-effectiveness ratios of one-way sensitivity analysis on vaccinating men and women compared to vaccinating women only. The vertical line represents the incremental cost-effectiveness ratio under base-case conditions. The sensitivity analysis range is displayed in parentheses next to each variable. Unequal penetration represents potential for lower (or higher) vaccine penetration in the highest risk groups, from 30% to 80% of target group, compared to 70% penetration in base case. QALY, quality-adjusted life-year.

predicted that broad-based immunization would decrease cervical cancer incidence by 17% (32). By using a disease-transmission model that predicts greater vaccine impact, we demonstrated that Pap testing vaccinated women every 3 or 4 years had a more powerful effect than a no-vaccine strategy (i.e., cost less and increased quality-adjusted life expectancy). With a vaccine program in place, moving from screening every 3 years to every 2 years cost >$100,000/QALY, while annual screening is not economically favorable (Figure 3). Given these data, with a vaccine program in place, physicians may be comfortable moving to less frequent screening.

We did not include in our analysis the effect of an HPV vaccine on several other cancers associated with HPV. We also did not examine the effect of vaccines targeting the nononcogenic HPV types most commonly associated with genital warts. Including the former would make the vaccine strategies appear to be even more cost-effective. The latter can be considered as a separate analysis, since a vaccine would offer little cross-protection between HPV types (5). Also, although some have suggested that lesion treatment protects against sequelae of future HPV infections (e.g., squamous intraepithelial lesions and cervical cancer) (30), we are not aware of evidence that supports this hypothesis, so we did not include it in our analysis. Including this potential benefit would diminish the cost-effectiveness of a future vaccine. Finally, our analysis does not examine targeted vaccination in men who are at high risk, for instance, in the community of men who have sex with men, in which HPV infection rates are higher than for the general population.

Although this analysis modeled vaccine programs in the United States, our results may have relevance for decision makers in less developed countries where public health resources are limited and cervical cancer death rates can be markedly higher than in the United States. These countries may have difficulty achieving high levels of vaccine penetration. However, because even modest vaccine coverage appears to substantially reduce cervical cancer cases, a partial vaccination program that includes specific populations might be more efficacious and cost-effective for these countries than alternative options, such as Pap or HPV screening.

Our analysis indicates that vaccinating 12-year-old girls with an HPV-16/18 vaccine would cost $14,583 /QALY, whereas vaccinating boys costs $442,039/QALY. In comparison, screening strategies of women for cervical cancer with Pap smears has been estimated to cost between $7,777 per life-year (LY) (quadrennial screening) and $166,000/LY (annual screening) and depends on the type of testing and prevalence of disease (31). Similarly, studies of hepatitis B vaccines have estimated costs from $4,800 to $16,000/QALY to selectively vaccinate at-risk populations versus universal infant vaccination or versus no vaccination, respectively (33).

Vaccine evaluations that do not include disease transmission can underestimate actual vaccine benefit (34–36). By modeling disease transmission by age category and risk grouping, we were able to estimate the effect of herd immunity, which we know from actual vaccine rollouts can be substantial (37,38). Prior cost-effectiveness analyses of potential HPV vaccines by our group (25) and others (32,39) have not included transmission by age category, multiple sexual activity subgroups, or the protective benefit of herd immunity. As a result, these analyses have likely underestimated the benefits of vaccination. In addition, previous approaches did not attempt to evaluate the cost-effectiveness of male vaccination. By modeling transmission by different age and risk groups, we also were able to address the issue of unequal vaccine penetration in high-risk groups, an important real world phenomenon.

Because an HPV vaccine is likely to be available in the future, public health officials will need to decide on HPV vaccine rollout strategies. Our analysis shows that a vaccine that protects against HPV-16/18 could be cost-effective and has the potential to substantially reduce cervical cancer rates. Additionally, under most scenarios, we showed that including men and boys in a vaccination program has a limited effect, which suggests that scarce healthcare resources could be used in a more productive manner. As ongoing clinical trials and vaccine development progress, we believe our analysis will provide public health officials with the tools needed to make optimal recommendations with limited resources.

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Mr. Taira is a fourth-year medical student at Stanford University and is affiliated with the Stanford Center for Primary Care and Outcomes Research. His research focuses on cost-effectiveness analyses and disease transmission dynamics within populations.

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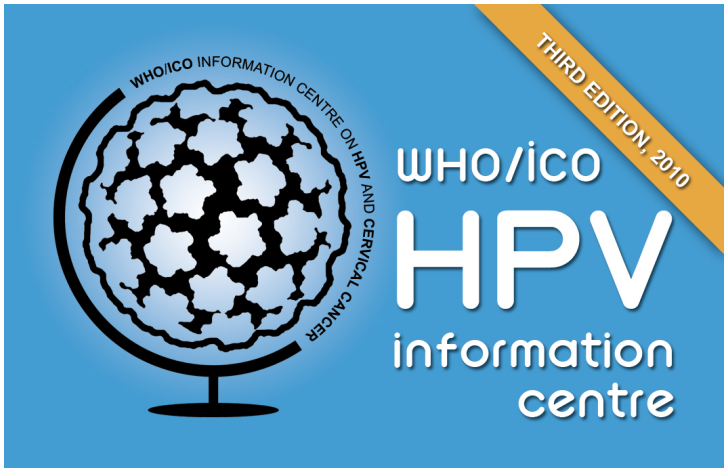

Human Papillomavirus and Related Cancers

Summary Report Update. September 15, 2010.

GUATEMALA

World Health Organization

ICO
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Available at www.who.int/hpvcentre

Preface

Preface to the third edition

Since the first edition of the HPV Information Centre, GLOBOCAN, one of the landmark products of the International Agency for Research on Cancer (IARC), serves as the reference source of cancer statistics. GLOBOCAN is a resource that provides on a regular basis the most accurate assessment of global cancer burden in the world. On June 1st 2010, the new edition of GLOBOCAN, GLOBOCAN 2008, was launched and new cancer estimates for 2008 are currently available.
This third edition of the HPV Information Centre incorporates the new burden estimates for all HPV-related cancers. In addition to the publicly available GLOBOCAN 2008, IARC has kindly provided the HPV Information Centre with age-specific estimates for HPV-related cancers which are also presented in this report.

Preface to the second edition

The available data on the epidemiology and prevention of HPV infection and HPV-related cancers at the country-specific level has grown substantially since the first edition of the HPV Information Centre in 2007.
This second edition reflects the continuous efforts to update our previous data and to expand the information to include new statistics. Thus, the user of the website (www.who.int/hpvcentre) will be able to find and manage new indicators on the burden of other HPV-related cancers (such as that of the vulva, vagina, anus, penis, oral cavity and pharynx), HPV in anogenital cancers, HPV in men, sexual and reproductive behaviour practices, HPV preventive strategies of cervical screening, HPV vaccine licensure and introduction, and male circumcision.
The HPV Information Centre team hopes that this update will be a useful resource to help formulate recommendations and public health interventions towards the prevention of cervical cancer and HPV-related diseases in each country.

Preface to the first edition

The main aim of this report is to summarize the information available on human papillomavirus (HPV) and cervical cancer at the country-specific level. The World Health Organization (WHO) in collaboration with the Institut Català d'Oncologia (ICO) have developed the WHO/ICO Information Centre on HPV and Cervical Cancer (HPV Information Centre) to evaluate the burden of disease in the country and to help facilitate stakeholders and relevant bodies of decision makers to formulate recommendations on cervical cancer prevention, including the implementation of the newly developed HPV vaccines.
Data aggregated are derived from data and official reports produced by the World Health Organization (WHO), International Agency for Research on Cancer (IARC), United Nations, The World Bank, and published literature. Indicators include relevant statistics on cancer, epidemiological determinants of cervical cancer such as demographics, socioeconomic factors and other risk factors, estimates on the burden of HPV infection, data on immunization and cervical cancer screening. These statistics are essential when planning and implementing cervical cancer prevention strategies. Therefore, we have integrated the most important information for each country into a report and on a website (www.who.int/hpvcentre) to provide a user-friendly tool to assess the best available information in each country.
The information presented here is intended as a resource for all who are working towards the prevention of cervical cancer.

Executive summary

Human papillomavirus (HPV) infection is now a well-established cause of cervical cancer and there is growing evidence of HPV being a relevant factor in other anogenital cancers (anus, vulva, vagina and penis) and head and neck cancers. HPV types 16 and 18 are responsible for about 70% of all cervical cancer cases worldwide. HPV vaccines that prevent against HPV 16 and 18 infection are now available and have the potential to reduce the incidence of cervical and other anogenital cancers.

This report provides key information for Guatemala on cervical cancer, other anogenital cancers and head and neck cancers, HPV-related statistics, factors contributing to cervical cancer, cervical cancer screening practices, HPV vaccine introduction, and other relevant immunization indicators. The report is intended to strengthen the guidance for health policy implementation of primary and secondary cervical cancer prevention strategies in the country.

Guatemala has a population of 3.80 millions women ages 15 years and older who are at risk of developing cervical cancer. Current estimates indicate that every year 1530 women are diagnosed with cervical cancer and 717 die from the disease. Cervical cancer ranks as the 1st most frequent cancer among women in Guatemala, and the 1st most frequent cancer among women between 15 and 44 years of age. About 33.2% of women in the general population are estimated to harbour cervical HPV infection at a given time., and % of invasive cervical cancers are attributed to HPVs 16 or 18.

Table 1: Key Statistics on Guatemala

Population			
Women at risk for cervical cancer (Female population aged >=15 yrs)			3.80 millions
Burden of cervical cancer and other HPV-related cancers			
Annual number of cervical cancer cases			1530
Annual number of cervical cancer deaths			717
Projected number of new cervical cancer cases in 2025*			2672
Projected number of cervical cancer deaths in 2025*			1284
Crude incidence rates per 100,000 population and year:		Male	Female
	Cervical cancer	-	21.8
	Anal cancer	-	-
	Vulva cancer	-	-
	Vaginal cancer	-	-
	Penile cancer	-	-
	Oral cavity	0.7	0.9
	Pharynx (excluding nasopharynx)	2.2	1.3
Burden of cervical HPV infection			
HPV prevalence (%) in the general population (among women with normal cytology)			33.2
Prevalence (%) of HPV 16 and/or HPV 18 among women with:			
	Normal cytology		5.5
	Low-grade cervical lesions (LSIL/CIN-1)		-
	High-grade cervical lesions (HSIL/ CIN-2 / CIN-3 / CIS)		-
	Cervical cancer		-
Other factors contributing to cervical cancer			
Smoking prevalence (%), women			3.9
Total fertility rate (live births per women)			4.5
Oral contraceptive use (%)			3.4
HIV prevalence (%), adults (15-49 years)			0.8
Sexual behaviour			
Median age at first sexual intercourse among men (25-54 years) / women (25-49 years)			- / 18.3
% of young men/women (15-24 years) who had sex before the age of 15			- / -
Cervical screening practices and recommendations			
Cervical cancer screening coverage, % (age and screening interval, reference)	42.7% (All women aged 15-49 yrs ever screened; ENSMI 2002)		
Screening ages (years)			25-59
Screening interval (years) or frequency of screens	Annual for ages 30-45; Every 2 years for ages 30-59; Annual for ages 25-59		
HPV vaccine			
HPV vaccine licensure			
	Bivalent Vaccine (Cervarix)		Yes
	Quadrivalent Vaccine (Gardasil/Silgard)		Yes
HPV vaccine introduction			
	HPV vaccine schedule		-
	Introduction in entire or part of the country		-
	Comment:		-
HPV vaccine recommendation			
	Recommendation for primary target population:		-
	Recommendation for "catch-up" population:		-
	Recommendation for vaccinating males:		-

*Projected burden in 2025 is estimated by applying current population forecasts for the country and assuming that current incidence/mortality rates of cervical cancer are constant over time.

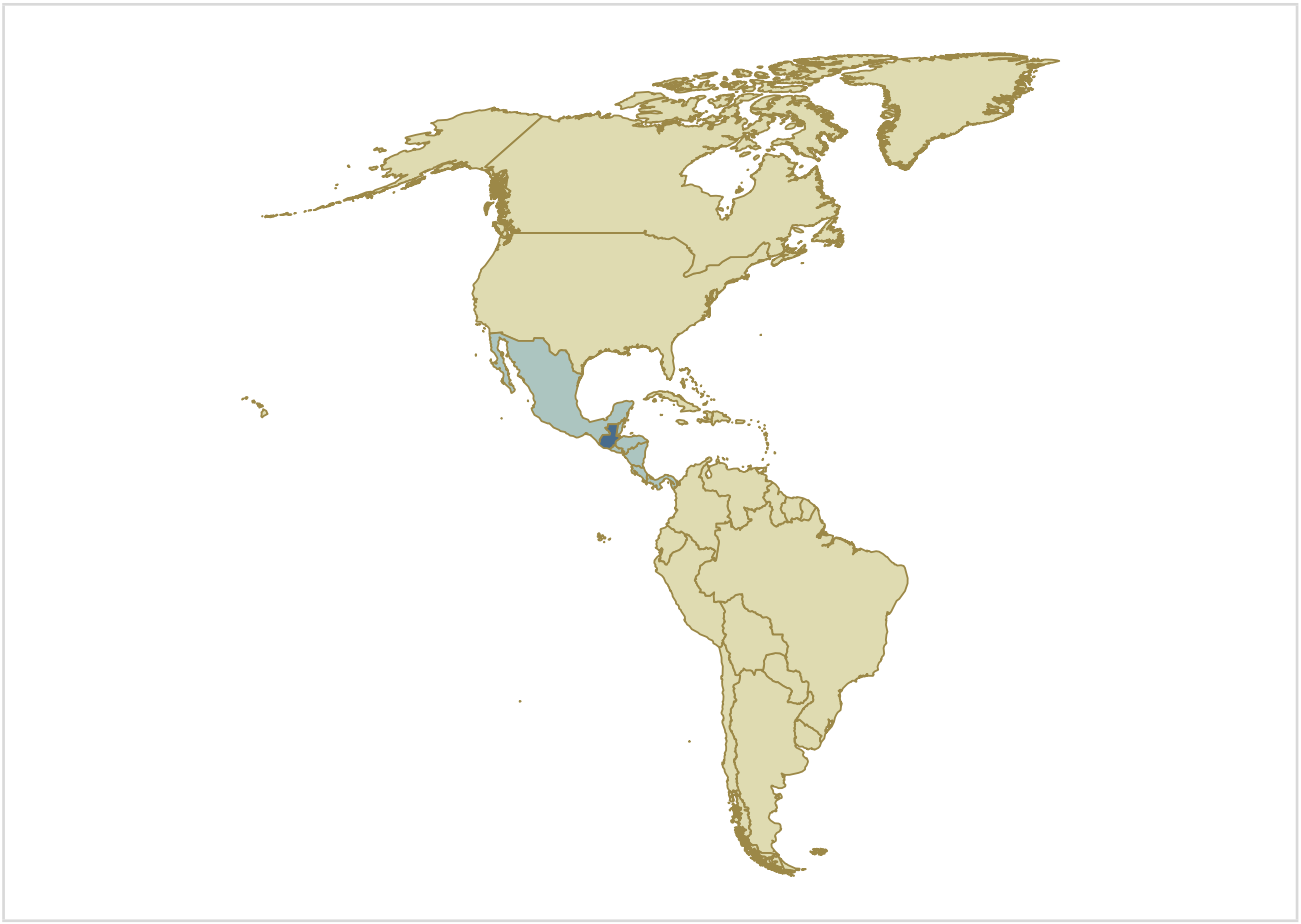
Contents

List of Figures

List of Tables

1 Introduction

Figure 1: Guatemala in Central America



The WHO/ICO Information Centre on HPV and Cervical Cancer (HPV Information Centre) aims to compile and centralize updated data and statistics on human papillomavirus (HPV) and related cancers. This report aims to summarize the data available to fully evaluate the burden of disease in Guatemala and to facilitate stakeholders and relevant bodies of decision makers to formulate recommendations on cervical cancer prevention. Data include relevant cancer statistic estimates, epidemiological determinants of cervical cancer such as demographics, socioeconomic factors, risk factors, burden of HPV infection, screening and immunization. The report is structured into the following sections:

Section 2 summarizes the socio-demographic profile of the country. For analytical purposes, Guatemala is classified in the geographical region of Central America (Figure 1, lighter blue), which is composed of the following countries:* Belize, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua and Panama. Throughout the report, Guatemala estimates will be complemented with corresponding estimates in the Central America region to provide the regional situation. When data are not available for Guatemala only regional estimates are shown.

Section 3 describes the current burden of invasive cervical cancer and other HPV-related cancers in Guatemala and the Central America region with estimates of prevalence, incidence and mortality rates.

Section 4 reports on the prevalence of HPV and HPV type-specific distribution in women with normal

*See http://unstats.un.org/unsd/methods/m49/m49regin.htm for more information.

cytology, pre-cancerous lesions and invasive cervical cancer. In addition, the burden of HPV in other anogenital cancers (anal, vulva, vagina and penis) and men are presented.

Section 5 describes factors that can modify the natural history of HPV and cervical carcinogenesis such as the use of smoking, parity, oral contraceptive use and co-infection with HIV.

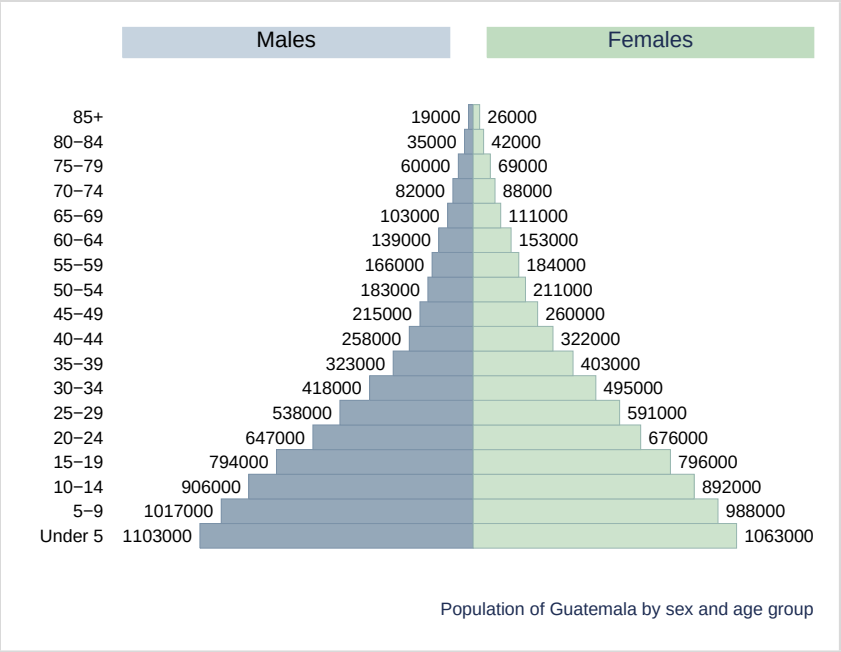
Section 6 describes sexual and reproductive health behaviour indicators that may be used as proxy measures of risk for HPV infection and anogenital cancers.

Section 7 presents preventive strategies that include basic characteristics and peformance of cervical cancer screening status, status of HPV vaccine licensure introduction, and recommendations in national immunization programs and the prevalence of male circumcision and condom use.

Section 8 presents data on immunization coverage and practices for selected vaccines. This information will be relevant for assessing the country's capacity to introduce and implement the new HPV vaccines. The data are periodically updated and posted on the WHO immunization surveillance, assessment and monitoring website. (http://www.who.int/immunization_monitoring/en/).

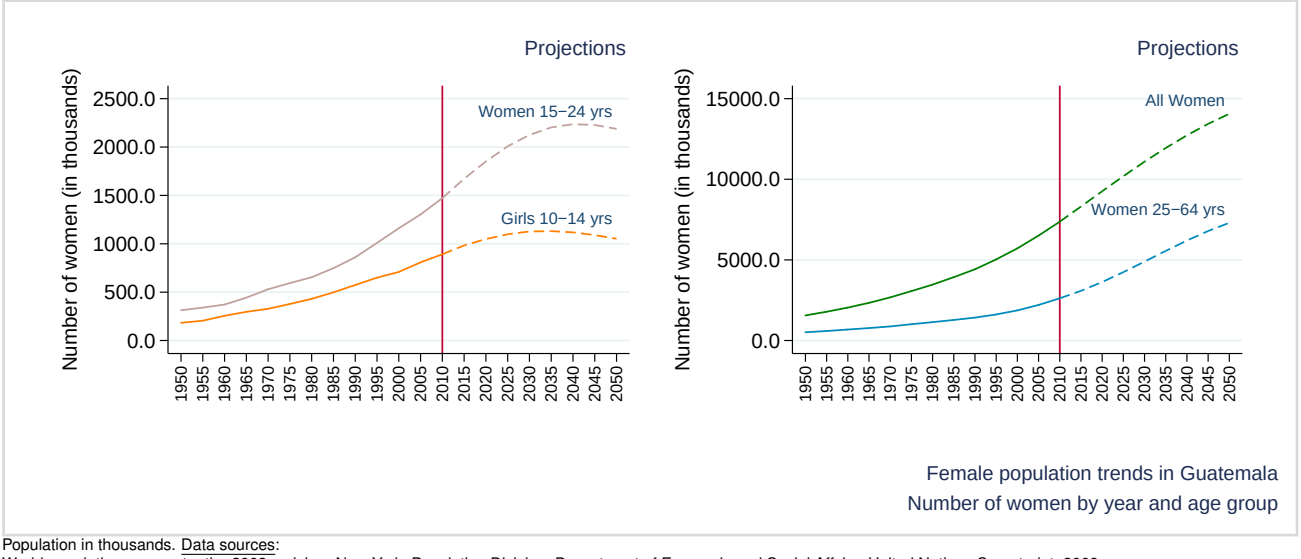
2 Demographic and socioeconomic factors

Figure 2: Population pyramid of Guatemala



Datapoint year 2010.
Data sources:
World population prospects: the 2008 revision. New York, Population Division, Department of Economic and Social Affairs, United Nations Secretariat, 2009.

Figure 3: Population trends of four selected age groups in Guatemala



Population in thousands. Data sources:
World population prospects: the 2008 revision. New York, Population Division, Department of Economic and Social Affairs, United Nations Secretariat, 2009.

Table 2: Sociodemographic indicators in Guatemala

Indicator	Male	Female	Total
Population in 1000s[1]	6202[a]	6508[a]	12710[a]
Population growth rate (%)[1]	-	-	2.47[b]
Median age (years)[1]	-	-	18.2[a]
Population living in urban areas (%)[2]	-	-	48[c]
Crude birth rate (births per 1000 population)[1]	-	-	33.3[b]
Crude death rate (deaths per 1000 population)[1]	-	-	5.7[b]
Life expectancy at birth (years):[3]	65[c]	71[c]	68[c]
Adult mortaliy rate:[3]	284[c]	163[c]	222[c]
Infant mortality rate (per 1000 live births):[3]	31[c]	30[c]	31[c]
Maternal mortality ratio (per 100,000 live births)[4]	-	-	290[a]
Neonatal mortality rate (per 1000 live births)[5]	-	-	19[d]
Under 5 mortality rate (per 1000 live births):[3]	41[c]	41[c]	41[c]
Gross national income per capita (PPP int $)[6]	-	-	4800[c]
Population living <$1 a day (%: PPP int $)[7]	-	-	13.5[e]
General government expenditure on health as % of total government expenditure[8]	-	-	15.7[a]
General government expenditure on health as % of total expenditure on health[8]	-	-	37.9[a]
Total expenditure on health as % of gross domestic product[8]	-	-	5.2[a]
Per capita total expenditure on health at average exchange rate (US$)[8]	-	-	132.0[a]
Per capita government expenditure on health at average exchange rate (US$)[8]	-	-	50.0[a]
Private expenditure on health as % of total expenditure on health[8]	-	-	62.1[a]
Density of physicians (per 10,000 population)[9]	-	-	9[e]
Number of physicians[9]	-	-	9965[e]
Adult (15 years and over) literacy rate (%)[10]	-	-	69.1[f]
Youth (15-24 years) literacy rate (%):[10]	88.1[g]	82.9[g]	85.5[g]
Net primary school enrollment ratio:[10]	96[e]	91[e]	-
Net secondary school enrollment ratio:[10]	39.7[e]	36.6[e]	-

Year of estimation: [a] 2005; [b] 2005-2010; [c] 2006; [d] 2004; [e] 2000-2006; [f] 2000-2005; [g] 2007;

Data notes and sources:

[1] World population prospects: the 2008 revision. New York, Population Division, Department of Economic and Social Affairs, United Nations Secretariat, 2009.

[2] World population prospects: the 2006 revision. New York, Population Division, Department of Economic and Social Affairs, United Nations Secretariat, 2007.

[3] Life tables for WHO Member States. Geneva, World Health Organization, 2006 (http://www.who.int/whosis/database/life_tables/life_tables.cfm, accessed 18 March 2008).

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[5] Neonatal and perinatal mortality: country, regional and global estimates 2004. Geneva, World Health Organization, 2007. (http://whqlibdoc.who.int/publications/2007/9789241596145_eng.pdf, accessed 18 March 2008).

[6] PPP int. $, purchasing power parity at international dollar rate.
GNI per capita 2007, atlas method and PPP. Washington, DC, World Bank, 2007.

[7] PPP int. $, purchasing power parity at international dollar rate.
World development indicators 2007. Washington, DC, International Bank for Reconstruction World Bank, 2007.

[8] Estimates updated using data from NHA reports, surveys, National Accounts series or information provided by contacts during national consultations.
National health accounts: country information. Geneva, World Health Organization, 2007 (http://www.who.int/nha/country/en/index.html, accessed 17 March 2008).

[9] Data refer to year prior to 2000.
Global atlas of the health workforce [online database]. Geneva, World Health Organization, 2008 (http://www.who.int/globalatlas/autologin/hrh_login.asp, accessed 17 March 2008).

[10] UNESCO Institute for Statistics Data Centre [online database]. Montreal, UNESCO Institute for Statistics, 2007 (http://stats.uis.unesco.org, accessed 16 March 2008).

3 Burden of HPV related cancers

3.1 Cervical cancer

Cancer of the cervix uteri is the second most common cancer among women worldwide, with an estimated 529,409 new cases and 274,883 deaths in 2008. About 86% of the cases occur in developing countries, representing 13% of female cancers. Worldwide, mortality rates of cervical cancer are substantially lower than incidence with a ratio of mortality to incidence to 52% (*IARC, GLOBOCAN 2008*). The majority of cases are squamous cell carcinoma and adenocarcinomas are less common. (*Vaccine 2006, Vol. 24, Supl 3; Vaccine 2008, Vol. 26, Supl 10; IARC Monographs 2007, Vol. 90*)

This section describes the current burden of invasive cervical cancer in Guatemala and the Central America region with estimates of annual number of new cases, deaths, and incidence and mortality rates.

3.1.1 Incidence

Table 3: Incidence of cervical cancer in Guatemala, Central America and the World

Indicator	Guatemala	Central America	World
Crude incidence rate[1]	21.8	20.6	15.8
Age-standardized incidence rate[1]	30.5	22.2	15.3
Cumulative risk (%). Ages 0-74 years[1]	2.9	2.2	1.6
Annual number of new cancer cases	1530	15606	529828

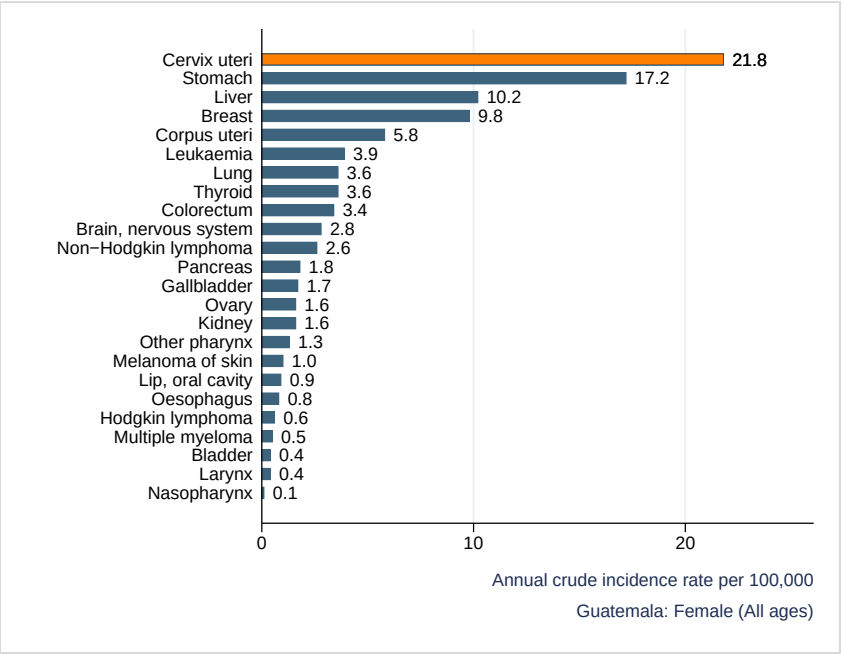
Standardized rates have been estimated using the direct method and the World population as the reference.
[1] Rates per 100,000 women per year.
Data sources:
IARC, Globocan 2008. (Specific methodology for Guatemala: National incidence was estimated from estimated national mortality for 2008 by modelling, using a set of age-, sex- and site-specific incidence mortality ratios obtained by the aggregation of recorded cancer registry data from Cuba, Costa Rica and Puerto Rico. For further details refer to http://globocan.iarc.fr/DataSource_and_methods.asp and http://globocan.iarc.fr/method/method.asp?country=320.)

Table 4: Incidence of cervical cancer in Guatemala by cancer registry

Cancer registry	Period	N cases[1]	Crude rate[2]	ASR[2]
No data available	-	-	-	-

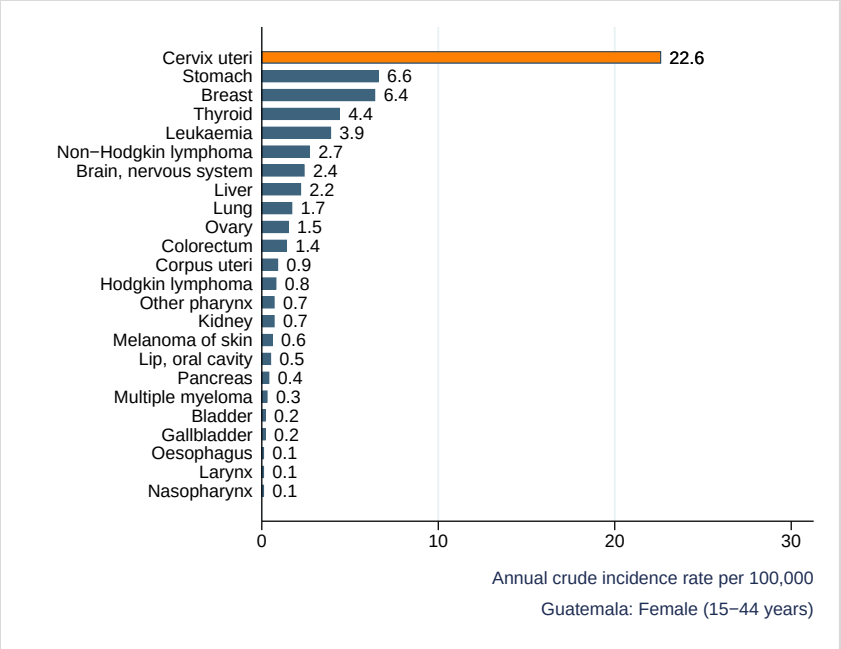
ASR: Age-standardized rate. Standardized rates have been estimated using the direct method and the World population as the reference.
[1] Accumulated number of cases during the period
[2] Rates per 100,000 women per year.
Data sources:
IARC, Cancer Incidence in 5 Continents, Vol IX

Figure 4: Incidence of cervical cancer compared to other cancers in women of all ages in Guatemala



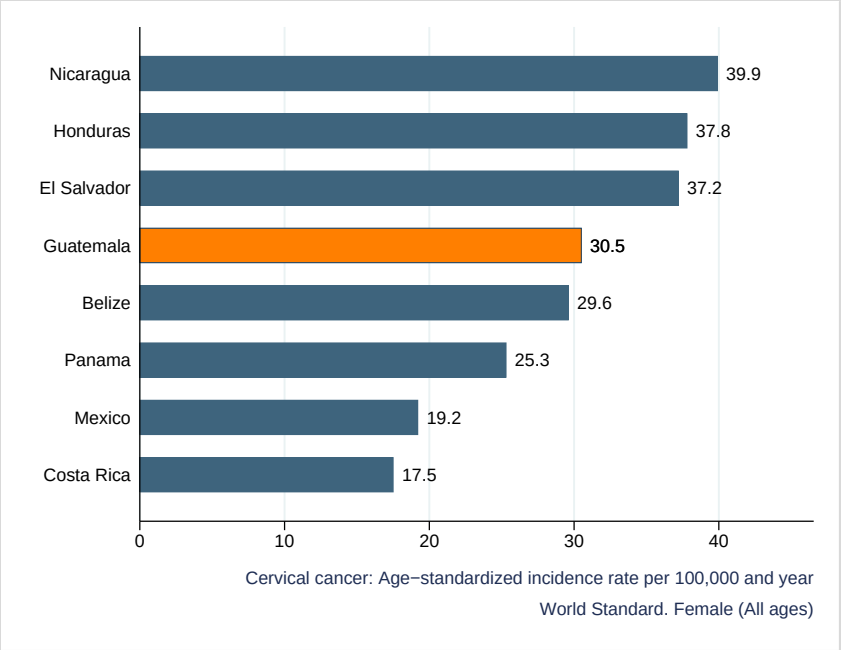
Data sources:
IARC, Globocan 2008. For specific estimation methodology refer to http://globocan.iarc.fr/DataSource_and_methods.asp.

Figure 5: Age-specific cervical cancer incidence compared to age-specific incidence of other cancers among women 15-44 years of age in Guatemala



Data sources:
IARC, Globocan 2008. Age-specific data from GLOBOCAN 2008 were obtained from IARC, personal communication. For specific estimation methodology refer to http://globocan.iarc.fr/DataSource_and_methods.asp.

Figure 6: Age-standardized incidence rates (ASR) of cervical cancer in countries of Central America



Rates per 100,000 women per year. ** No rates are available
Data sources:
IARC, Globocan 2008. Age-specific data from GLOBOCAN 2008 were obtained from IARC, personal communication.
For specific estimation methodology refer to http://globocan.iarc.fr/DataSource_and_methods.asp.

Table 5: Age-standardized incidence rates of cervical cancer by histological type and cancer registry in Guatemala

		Carcinoma			
Cancer registry	**Period**	**Squamous**	**Adeno**	**Other**	**Unspec.**
No data available	-	-	-	-	-

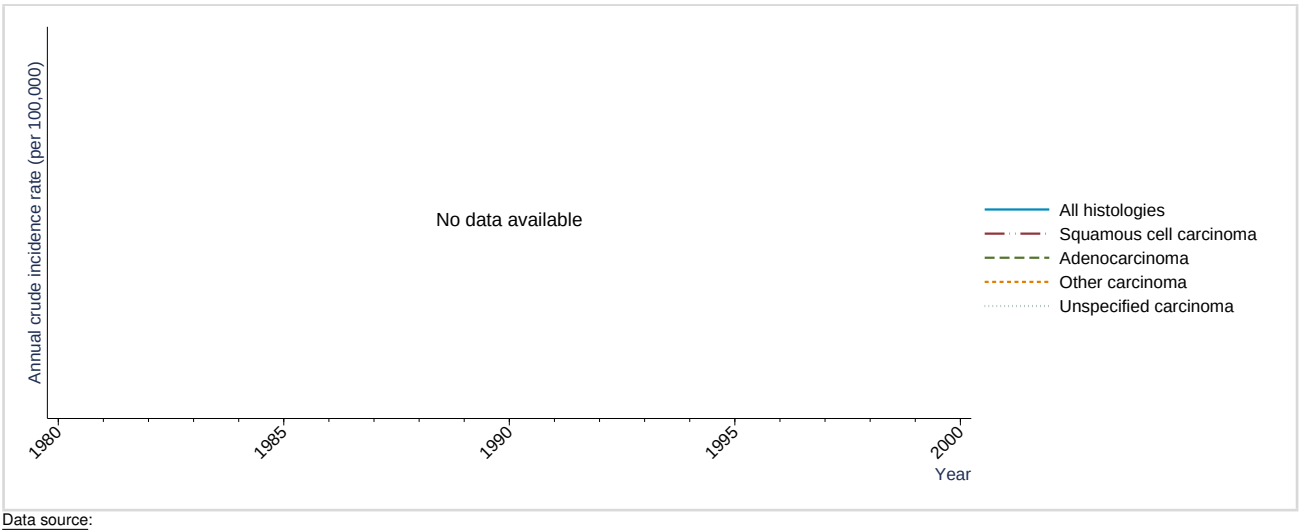
Standardized rates have been estimated using the direct method and the World population as the reference.
Rates per 100,000 women per year.
Data sources:
IARC, Cancer Incidence in 5 Continents, Vol IX

Table 6: Percentage distribution of microscopically verified cases of cervical cancer by histological type and cancer registry in Guatemala

		Histology				Number of cases	
Cancer registry	**Period**	**Squamous**	**Adeno**	**Other**	**Unspec.**	**MV cases**	**Total cases**
No data available	-	-	-	-	-	-	-

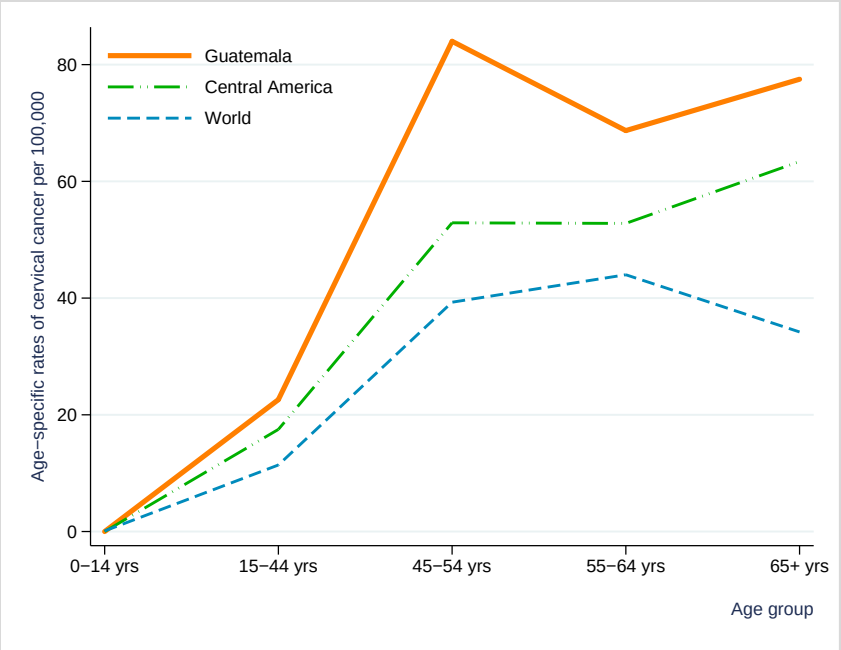
Standardized rates have been estimated using the direct method and the World population as the reference.
Accumulated number of cases during the period.
MV: Microscopically Verified.
Data sources:
IARC, Cancer Incidence in 5 Continents, Vol IX

Figure 7: Time trends of age-truncated (15-85 years) incidence rates of cervical cancer by histological type in Guatemala



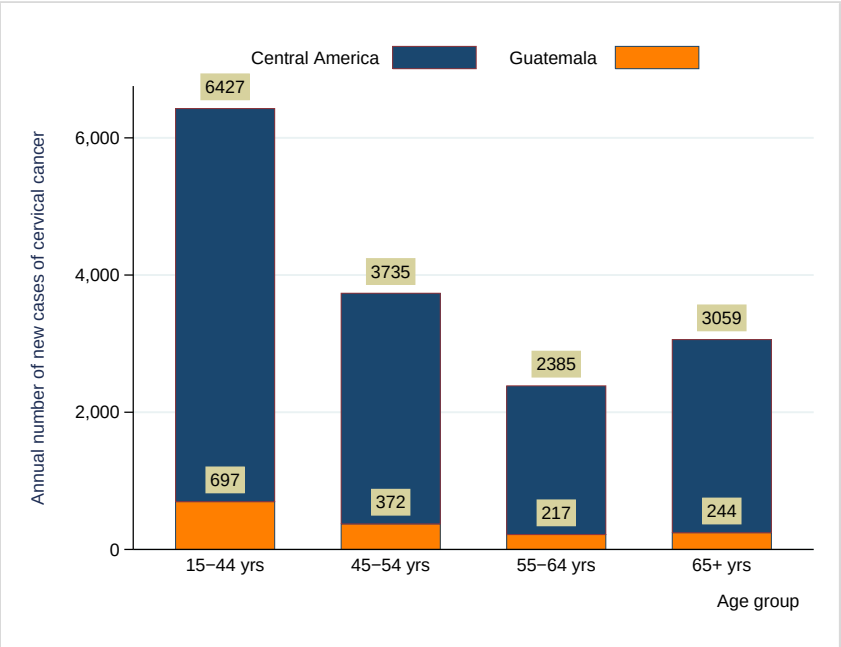
Data source:
IARC, Cancer Incidence in 5 Continents, Vol I-VIII

Figure 8: Age-specific incidence rates of cervical cancer in Guatemala compared to estimates in Central America and the World



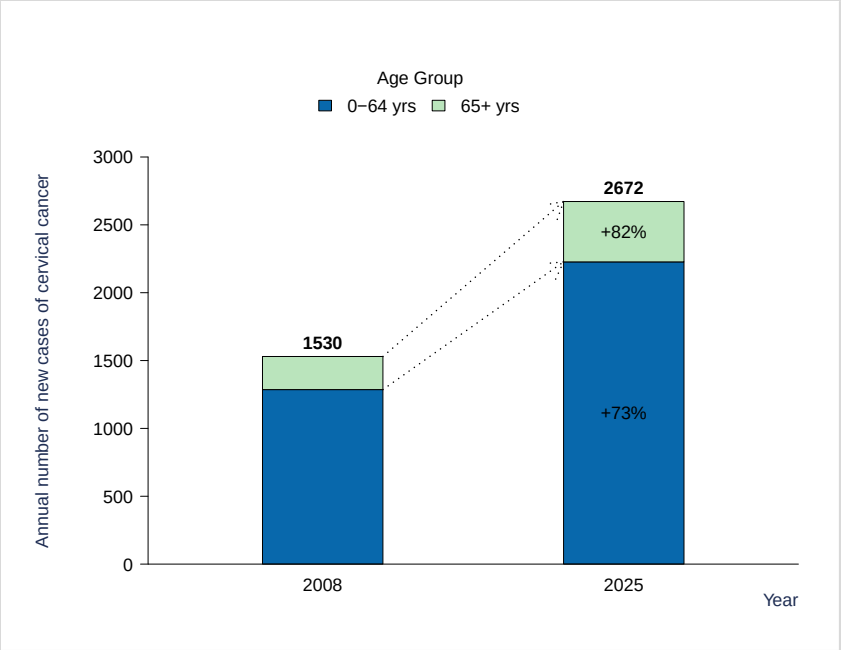
Rates per 100,000 women per year.
Data sources:
IARC, Globocan 2008. Age-specific data from GLOBOCAN 2008 were obtained from IARC, personal communication.
For specific estimation methodology refer to http://globocan.iarc.fr/DataSource_and_methods.asp.

Figure 9: Annual number of new cases of cervical cancer by age group in Guatemala and Central America



Data sources:
IARC, Globocan 2008. Age-specific data from GLOBOCAN 2008 were obtained from IARC, personal communication.
For specific estimation methodology refer to http://globocan.iarc.fr/DataSource_and_methods.asp.

Figure 10: Estimated number of new cases of cervical cancer in Guatemala by age group, in 2008 and projected in 2025



Projected burden in 2025 is estimated by applying current population forecasts for the country and assuming that current incidence rates of cervical cancer are constant over time.
Data sources:
IARC, Globocan 2008.

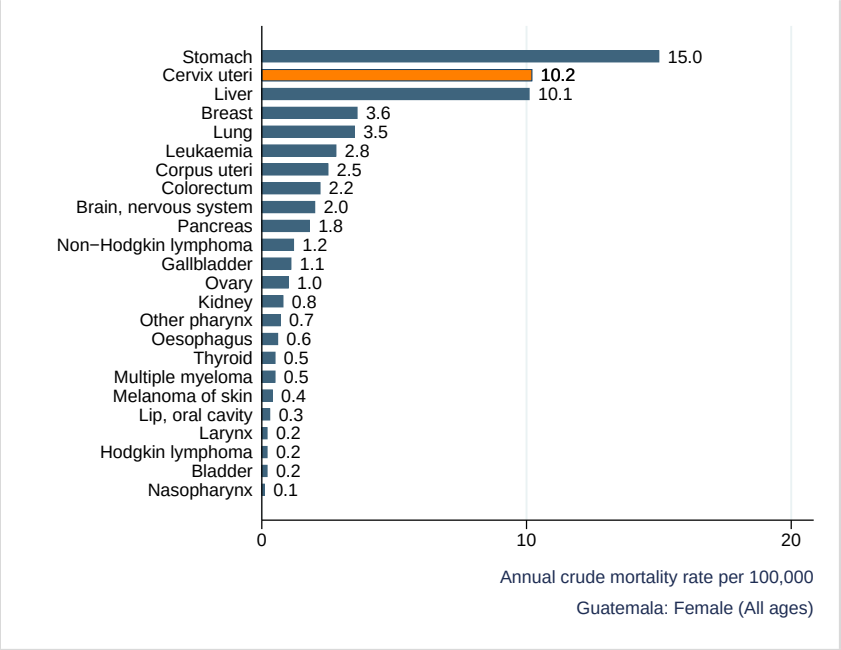
3.1.2 Mortality

Table 7: Mortality of cervical cancer in Guatemala, Central America and the World

Indicator	Guatemala	Central America	World
Crude mortality rate[1]	10.2	10.1	8.2
Age-standardized mortality rate[1]	15.2	11.1	7.8
Cumulative risk (%) ages 0-74 years[1]	1.5	1.2	0.9
Annual number of deaths	717	7631	275128

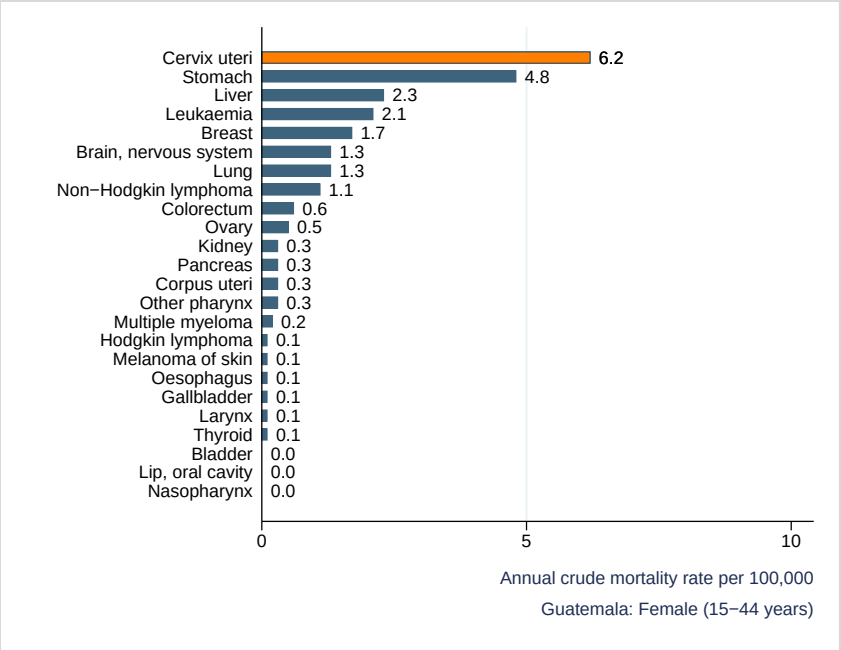
Standardized rates have been estimated using the direct method and the World population as the reference.
[1] Rates per 100,000 women per year.
Data sources:
IARC, Globocan 2008. (Specific methodology for Guatemala: Estimated national mortality by sex for 2008 (source WHO Mortality Data), was partitioned by site and age using national mortality data for 2005-2006 (source WHO Mortality Data). For further details refer to http://globocan.iarc.fr/DataSource_and_methods.asp and http://globocan.iarc.fr/method/method.asp?country=320.)

Figure 11: Cervical cancer mortality compared to other cancers in women of all ages in Guatemala



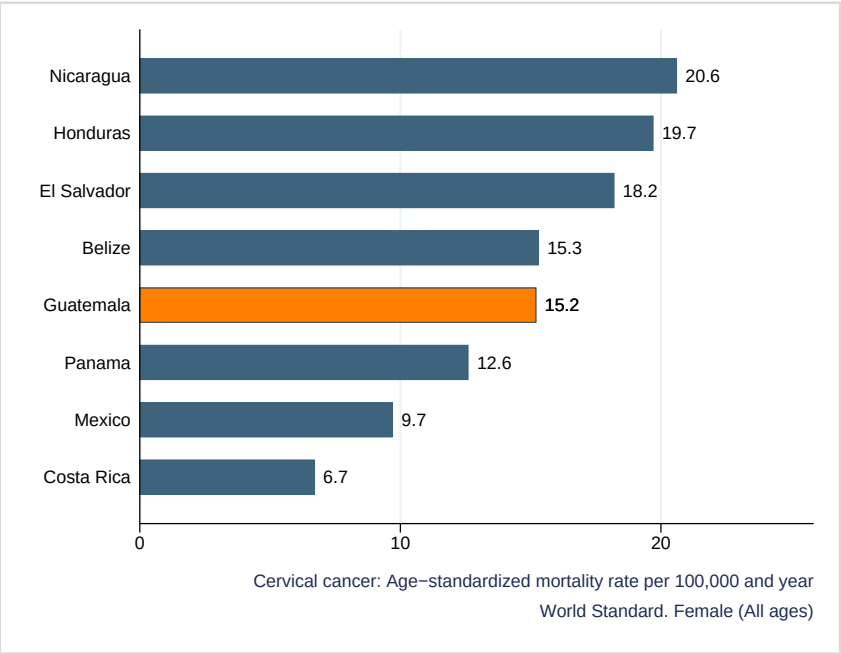
Data sources:
IARC, Globocan 2008. For specific estimation methodology refer to http://globocan.iarc.fr/DataSource_and_methods.asp.

Figure 12: Age-specific mortality rates of cervical cancer compared to age-specific mortality rates of other cancers among women 15-44 years of age in Guatemala



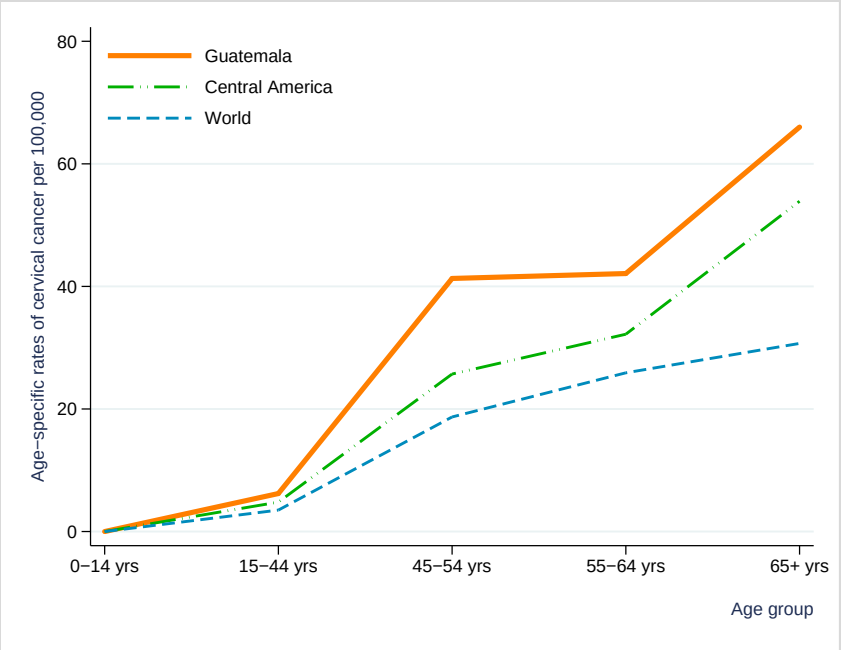
Data sources:
IARC, Globocan 2008. Age-specific data from GLOBOCAN 2008 were obtained from IARC, personal communication.
For specific estimation methodology refer to http://globocan.iarc.fr/DataSource_and_methods.asp.

Figure 13: Age-standardized (ASR) mortality rates of cervical cancer in countries of Central America



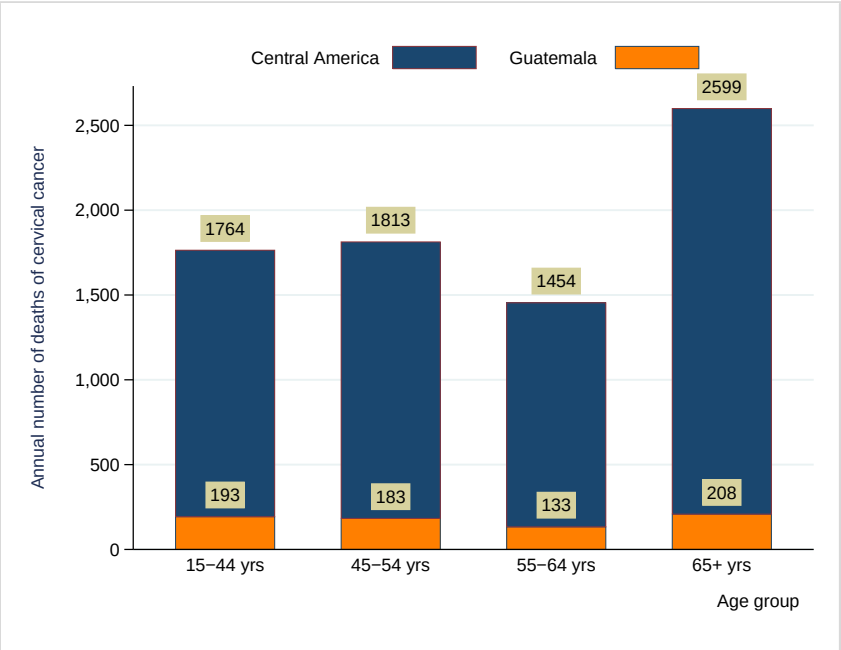
Rates per 100,000 women per year. ** No rates are available
Data sources:
IARC, Globocan 2008. Age-specific data from GLOBOCAN 2008 were obtained from IARC, personal communication.
For specific estimation methodology refer to http://globocan.iarc.fr/DataSource_and_methods.asp.

Figure 14: Age-specific mortality rates of cervical cancer in Guatemala compared to estimates in Central America and the World



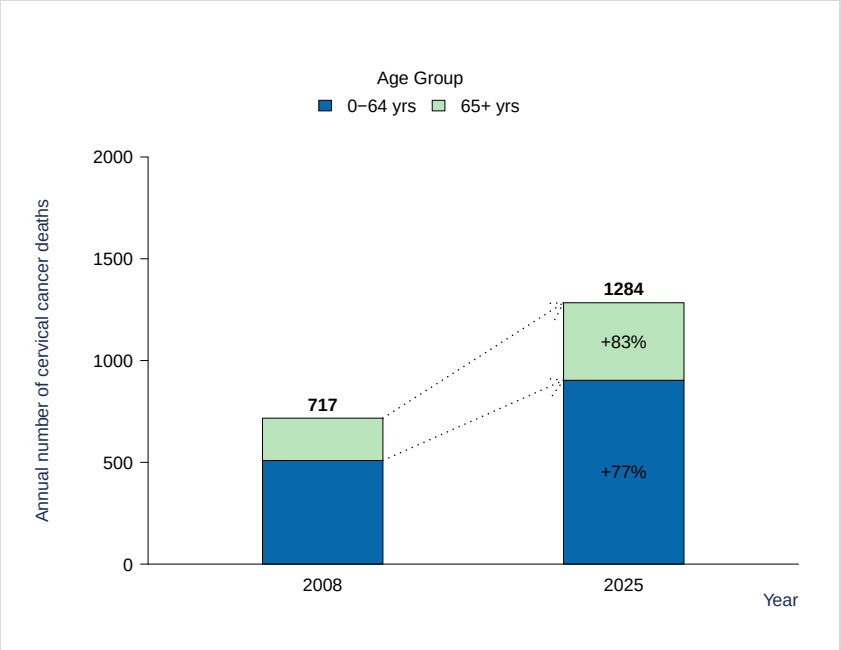
Rates per 100,000 women per year.
Data sources:
IARC, Globocan 2008. Age-specific data from GLOBOCAN 2008 were obtained from IARC, personal communication.
For specific estimation methodology refer to http://globocan.iarc.fr/DataSource_and_methods.asp.

Figure 15: Annual number of deaths of cervical cancer by age group in Guatemala and Central America



Data sources:
IARC, Globocan 2008. Age-specific data from GLOBOCAN 2008 were obtained from IARC, personal communication.
For specific estimation methodology refer to http://globocan.iarc.fr/DataSource_and_methods.asp.

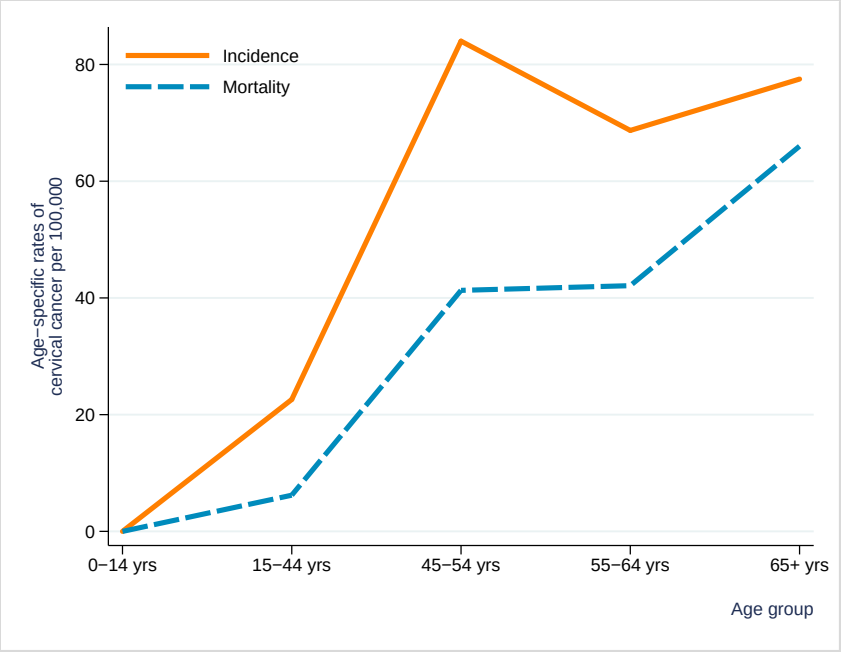
Figure 16: Estimated number of deaths of cervical cancer in Guatemala by age group, in 2008 and projected in 2025



Projected burden in 2025 is estimated by applying current population forecasts for the country and assuming that current incidence rates of cervical cancer are constant over time.
Data sources:
IARC, Globocan 2008.

3.1.3 Comparison of incidence and mortality

Figure 17: Comparison of age-specific incidence and mortality rates of cervical cancer in Guatemala



Rates per 100,000 women per year.
Data sources:
IARC, Globocan 2008. Age-specific data from GLOBOCAN 2008 were obtained from IARC, personal communication.
For specific estimation methodology refer to http://globocan.iarc.fr/DataSource_and_methods.asp.

3.2 Anogenital cancers other than the cervix

Data on the role of HPV in anogenital cancers other than the cervix are limited, but there is an increasing body of evidence strongly linking HPV DNA with cancers of the anus, vulva, vagina, and penis. Although these cancers are much less frequent compared to cancer of the cervix, their association with HPV make them potentially preventable and subject to similar preventative strategies as those for cervical cancer.
(*Vaccine 2006, Vol. 24, Supl 3; Vaccine 2008, Vol. 26, Supl 10; IARC Monographs 2007, Vol. 90*)

3.2.1 Anal cancer

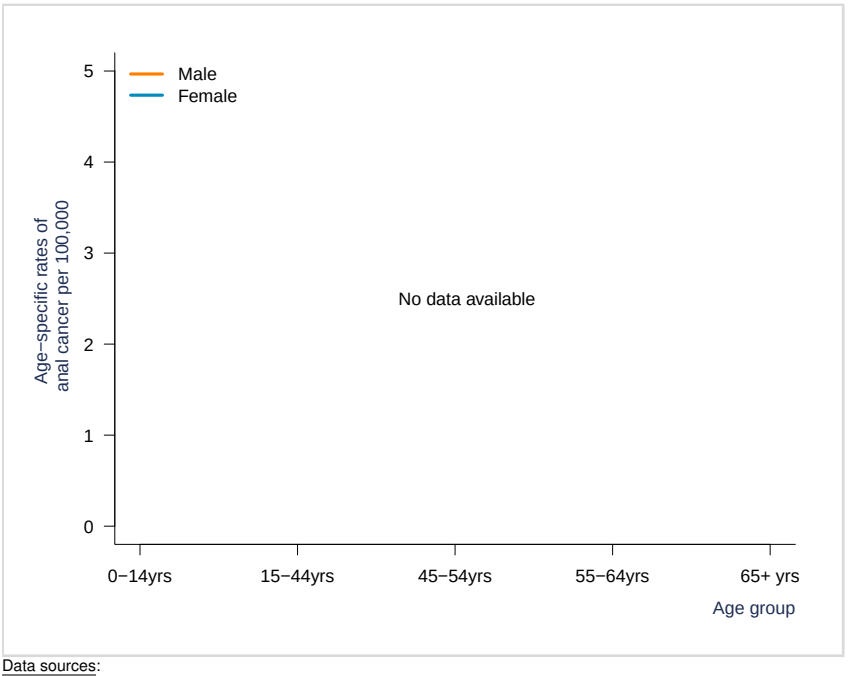
Cancer of the anus is rare, with an estimated 99,000 new cases in 2002, 40% of cases in men and 60% in women. Incidence has been increasing in both men and women over the last five decades, and incidence is particularly high among populations of men who have sex with men (MSM) and those who are HIV-infected. These cancers are predominantly squamous cell carcinoma, adenocarcinomas, or basaloid and cloacogenic carcinomas.

Table 8: Incidence of anal cancer by cancer registry and sex in Guatemala

		MALE			FEMALE		
Cancer registry	**Period**	**N cases[1]**	**Crude rate[2]**	**ASR[2]**	**N cases[1]**	**Crude rate[3]**	**ASR[3]**
No data available	-	-	-	-	-	-	-

ASR: Age-standardized rate. Standardized rates have been estimated using the direct method and the World population as the reference.
[1] Accumulated number of cases during the period
[2] Rates per 100,000 men per year.
[3] Rates per 100,000 women per year.
Data sources:
IARC, Cancer Incidence in 5 Continents, Vol IX

Figure 18: Incidence rates of anal cancer by age group in Guatemala



Data sources:
Cancer Incidence in Five Continents Vol. IX

3.2.2 Vulvar Cancer

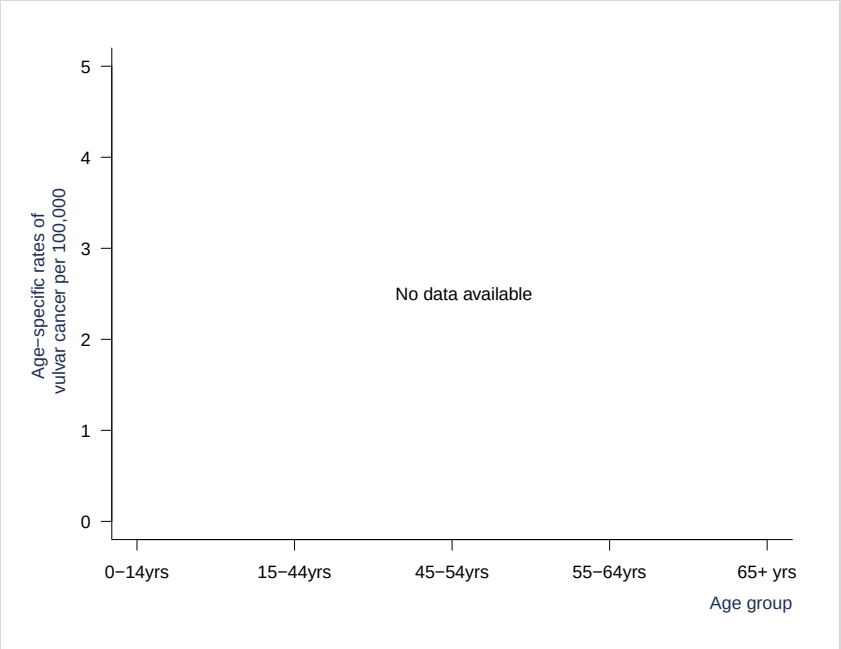
Cancer of the vulva is rare among women worldwide, with an estimated 26,800 new cases in 2002, representing 3% of all gynaecologic cancers. Worldwide, about 60% of all vulvar cancer cases occur in developed countries, indicating the limited impact of cervical screening programmes to prevent vulvar and vaginal cancers. Vulvar cancer is common in older women with approximately 66% of cases diagnosed at >=70 years. The majority of vulvar cancer cases are squamous cell carcinoma (90%), followed by melanoma, Bartholin gland carcinoma, basal cell carcinoma, verrucous carcinoma, and Paget's disease.

Table 9: Incidence of vulvar cancer by cancer registry in Guatemala

Cancer registry	Period	N cases[1]	Crude rate[2]	ASR[2]
No data available	-	-	-	-

ASR: Age-standardized rate. Standardized rates have been estimated using the direct method and the World population as the reference.
[1] Accumulated number of cases during the period
[2] Rates per 100,000 women per year.
Data sources:
IARC, Cancer Incidence in 5 Continents, Vol IX

Figure 19: Incidence rates of vulvar cancer by age group in Guatemala



Data sources:
Cancer Incidence in Five Continents Vol. IX

3.2.3 Vaginal cancer

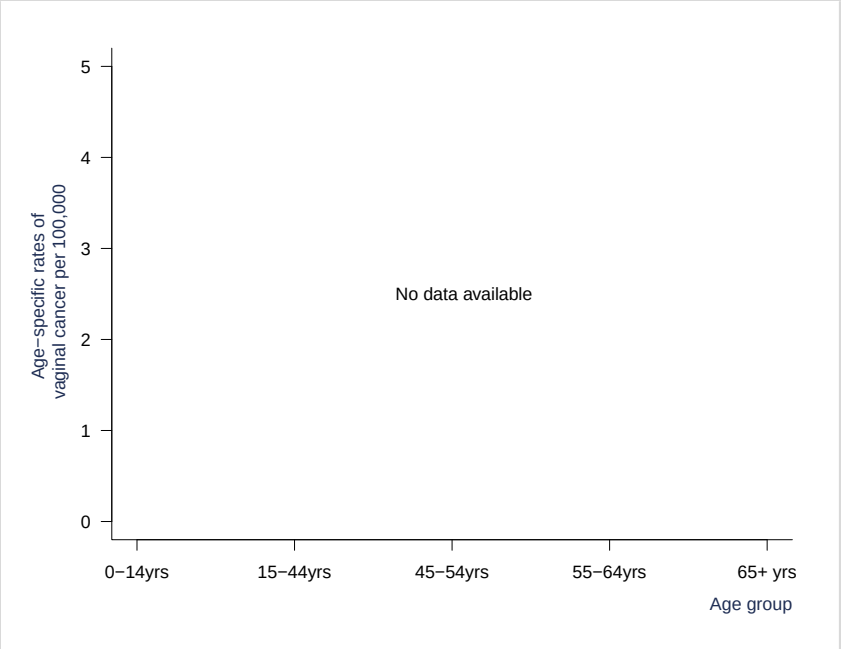
Cancer of the vagina is a rare cancer, with an estimated 13,200 of new cases in 2002, representing 2% of all gynaecologic cancers. Similar to cervical cancer, the majority of vaginal cancer cases (68%) occur in developing countries. Most vaginal cancers are squamous cell carcinoma (90%), followed by clear cell adenocarcinomas and melanoma. There are few data available on vaginal cancers, which are primarily reported in developed countries, and in some settings, metastatic cervical cancer can be misclassified as cancer of the vagina. Vaginal cancer is diagnosed primarily in older women (>=65 years) with a median age at diagnosis of 69 years, and the incidence of carcinoma in situ is diagnosed between the ages of 55 and 70 years.

Table 10: Incidence of vaginal cancer by cancer registry in Guatemala

Cancer registry	Period	N cases[1]	Crude rate[2]	ASR[2]
No data available	-	-	-	-

ASR: Age-standardized rate. Standardized rates have been estimated using the direct method and the World population as the reference.
[1] Accumulated number of cases during the period
[2] Rates per 100,000 women per year.
Data sources:
IARC, Cancer Incidence in 5 Continents, Vol IX

Figure 20: Incidence rates of vaginal cancer by age group in Guatemala



Data sources:
Cancer Incidence in Five Continents Vol. IX

3.2.4 Penile cancer

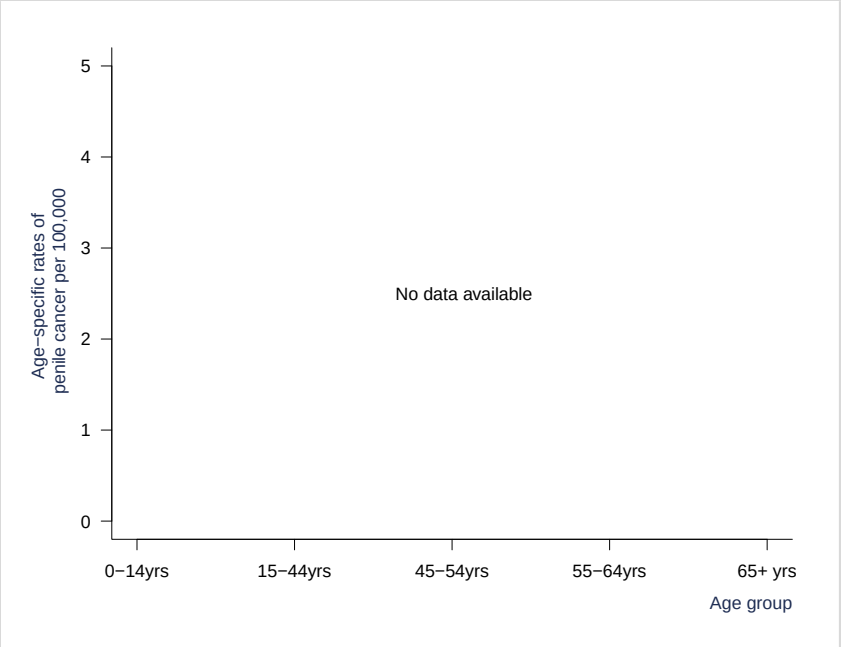
Cancer of the penis represents less than 0.5% of cancers in men. Incidence rates are less than 1 per 100,000 in Western countries, with higher rates found in Latin America such as Brazil, Colombia, and Peru, Uganda, and specific regions in India and Thailand. A geographical correlation between the incidence of cancer of the penis and cervix and the concordance of these two cancers in married couples suggested the common aetiology of HPV. Cancers of the penis are primarily of the squamous cell histological type.

Table 11: Incidence of penile cancer by cancer registry in Guatemala

Cancer registry	Period	N cases[1]	Crude rate[2]	ASR[2]
No data available	-	-	-	-

ASR: Age-standardized rate. Standardized rates have been estimated using the direct method and the World population as the reference.
[1] Accumulated number of cases during the period
[2] Rates per 100,000 men per year.
Data sources:
IARC, Cancer Incidence in 5 Continents, Vol IX

Figure 21: Incidence rates of penile cancer by age group in Guatemala



Data sources:
Cancer Incidence in Five Continents Vol. IX

3.3 Head and neck cancers

About 400,000 new cases of the oral cavity and the pharynx (excluding nasopharynx) and 223,000 deaths occurred worldwide in 2008. Two-thirds of cases occurred in developing countries. The majority of head and neck cancers is associated with high tobacco and alcohol consumption. However, there are about 15-20% of head and neck cancer cases that are associated with HPV and there is growing evidence that these HPV-related cases, particularly oral pharyngeal cancers, are associated with sexual behaviour including the practice of oral sex.

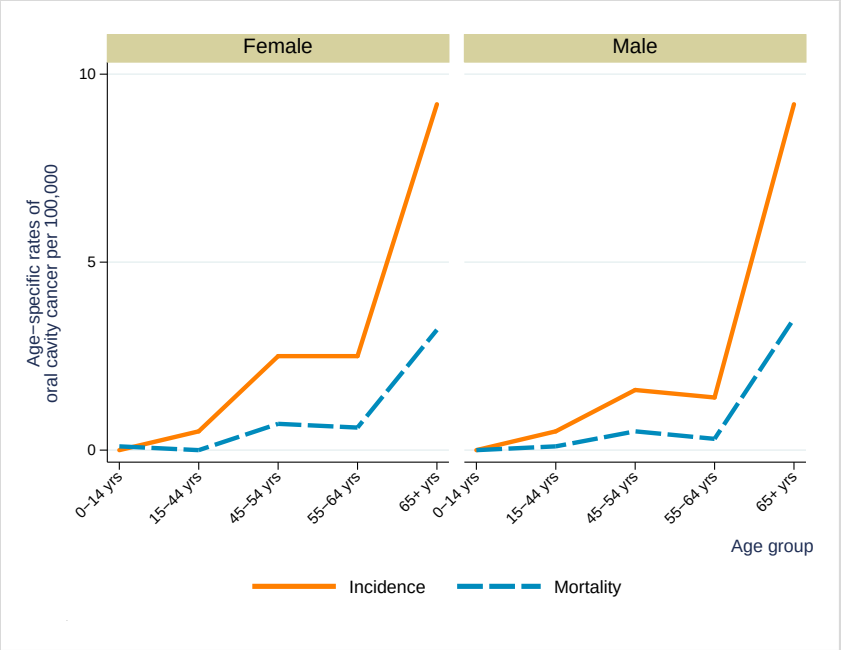
3.3.1 Oral cavity

Table 12: Incidence and mortality of cancer of the oral cavity by sex in Guatemala, Central America and the World

Indicator	MALE			FEMALE		
	Guatemala	Central America	World	Guatemala	Central America	World
INCIDENCE						
Crude incidence rate[1]	0.7	2.2	5.0	0.9	1.5	2.8
Age-standardized incidence rate[1]	1.1	2.7	5.3	1.4	1.7	2.6
Cumulative risk (%) ages 0-74 years[1]	0.1	0.3	0.6	0.2	0.2	0.3
Annual number of new cancer cases	50	1616	170903	63	1128	92958
MORTALITY						
Crude mortality rate[1]	0.2	0.7	2.4	0.3	0.5	1.3
Age-standardized mortality rate[1]	0.4	0.9	2.6	0.4	0.5	1.2
Cumulative risk (%) ages 0-74 years[1]	0.0	0.1	0.3	0.0	0.1	0.1
Annual number of deaths	16	517	83254	18	348	44697

Standardized rates have been estimated using the direct method and the World population as the reference.
[1] Male: Rates per 100,000 men per year. Female: Rates per 100,000 women per year.
Data sources:
IARC, Globocan 2008. (Specific methodology for Guatemala: A) Incidence. National incidence was estimated from estimated national mortality for 2008 by modelling, using a set of age-, sex- and site-specific incidence mortality ratios obtained by the aggregation of recorded cancer registry data from Cuba, Costa Rica and Puerto Rico. B) Mortality. Estimated national mortality by sex for 2008 (source WHO Mortality Data), was partitioned by site and age using national mortality data for 2005-2006 (source WHO Mortality Data). For further details refer to http://globocan.iarc.fr/DataSource_and_methods.asp and http://globocan.iarc.fr/method/method.asp?country=320.)

Figure 22: Comparison of incidence and mortality rates of oral cavity cancer by age group in Guatemala



Data sources:
IARC, Globocan 2008. Age-specific data from GLOBOCAN 2008 were obtained from IARC, personal communication.
For specific estimation methodology refer to http://globocan.iarc.fr/DataSource_and_methods.asp.

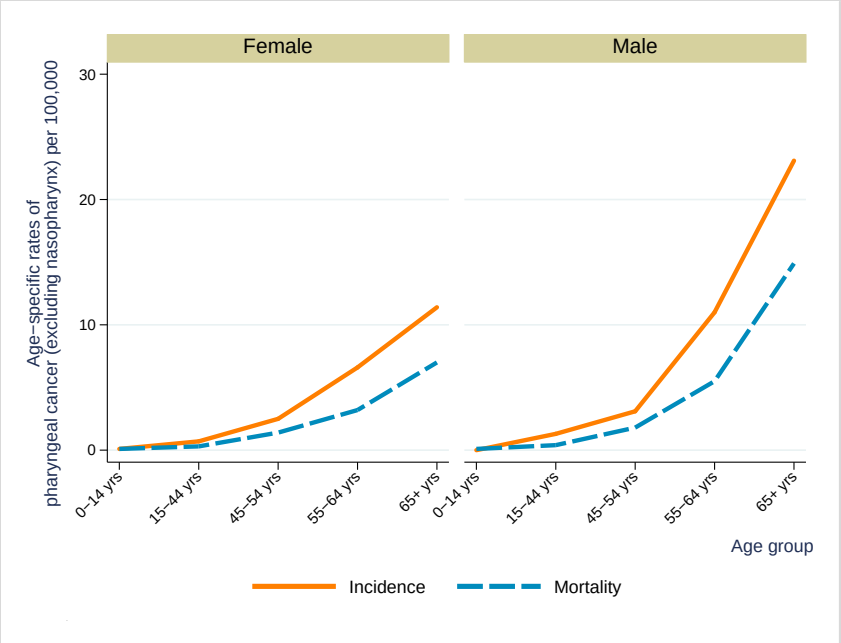
3.3.2 Pharynx (excluding nasopharynx)

Table 13: Incidence and mortality of cancer of the pharynx (excluding nasopharynx) by sex in Guatemala, Central America and the World

Indicator	MALE			FEMALE		
	Guatemala	Central America	World	Guatemala	Central America	World
INCIDENCE						
Crude incidence rate[1]	2.2	1.2	3.2	1.3	0.5	0.8
Age-standardized incidence rate[1]	3.5	1.5	3.4	2.1	0.5	0.8
Cumulative risk (%) ages 0-74 years[1]	0.4	0.2	0.4	0.2	0.1	0.1
Annual number of new cancer cases	145	868	107941	93	353	27744
MORTALITY						
Crude mortality rate[1]	1.2	0.7	2.2	0.7	0.3	0.6
Age-standardized mortality rate[1]	1.8	0.8	2.4	1.0	0.3	0.5
Cumulative risk (%) ages 0-74 years[1]	0.2	0.1	0.3	0.1	0.0	0.1
Annual number of deaths	80	507	76363	49	208	19095

Standardized rates have been estimated using the direct method and the World population as the reference.
[1] Male: Rates per 100,000 men per year. Female: Rates per 100,000 women per year.
Data sources:
IARC, Globocan 2008. (Specific methodology for Guatemala: A) Incidence. National incidence was estimated from estimated national mortality for 2008 by modelling, using a set of age-, sex- and site-specific incidence mortality ratios obtained by the aggregation of recorded cancer registry data from Cuba, Costa Rica and Puerto Rico. B) Mortality. Estimated national mortality by sex for 2008 (source WHO Mortality Data), was partitioned by site and age using national mortality data for 2005-2006 (source WHO Mortality Data). For further details refer to http://globocan.iarc.fr/DataSource_and_methods.asp and http://globocan.iarc.fr/method/method.asp?country=320.)

Figure 23: Comparison of incidence and mortality rates of pharyngeal cancer by age group in Guatemala



Data sources:
IARC, Globocan 2008. Age-specific data from GLOBOCAN 2008 were obtained from IARC, personal communication. For specific estimation methodology refer to http://globocan.iarc.fr/DataSource_and_methods.asp.

4 HPV related statistics

Human papillomavirus infection is commonly found in the anogenital tract of men and women with and without clinical lesions. The aetiological role of HPV infection among women with cervical cancer is well-established, and there is growing evidence of its central role in other anogenital sites This section presents the HPV burden at each of the anogenital tract sites. The methodologies used to compile the information on HPV burden are derived from systematic reviews and meta-analyses of the literature. Due to the limitations of HPV DNA detection methods and study designs used, these data should be interpreted cautiously and used only as a guidance to assess the burden of HPV infection in the population. (*Vaccine 2006, Vol. 24, Supl 3; Vaccine 2008, Vol. 26, Supl 10; IARC Monographs 2007, Vol. 90*)

4.1 HPV burden in women with normal cytology, precancerous cervical lesions or invasive cervical cancer

The statistics shown in this section focus on HPV infection in the cervix uteri. HPV cervical infection results in cervical morphological lesions ranging from normalcy (cytologically normal women) to different stages of precancerous lesions (CIN-1, CIN-2, CIN-3/CIS) and invasive cervical cancer. HPV infection is measured by means of HPV DNA detection in cervical cells (fresh tissue, paraffin embedded or exfoliated cells).

The prevalence of HPV increases with severity of the lesion. HPV causes virtually 100% of cases of cervical cancer, and an underestimation of HPV prevalence in cervical cancer is most likely due to the limitations of study methodologies. Worldwide, HPV-16 and 18, the two vaccine-preventable types. contribute to over 70% of all cervical cancer cases, between 41% and 67% of high-grade cervical lesions and 16-32% of low-grade cervical lesions. After HPV-16/18, the six most common HPV types are the same in all world regions, namely 31, 33, 35, 45, 52 and 58; these account for an additional 20% of cervical cancers worldwide (*Clifford G et al. Vaccine 2006;24(S3):26-34*).

HPV is also responsible for other benign genital infections such as recurrent juvenile respiratory papillomatosis and genital warts, both mainly caused by HPV types 6 and 11 (*Lacey CJ et al. Vaccine 2006; 24(S3):35-41*).

4.1.1 Terminology

Cytologically normal women

No abnormal cells are observed on the surface of their cervix upon cytology.

Cervical Intraepithelial Neoplasia (CIN) / Squamous Intraepithelial Lesions (SIL)

SIL and CIN are two commonly used terms to describe precancerous lesions or the abnormal growth of squamous cells observed in the cervix. SIL is an abnormal result derived from cervical cytological screening or Pap smear testing. CIN is a histological diagnosis made upon analysis of cervical tissue obtained by biopsy or surgical excision.

Low-grade cervical lesions (LSIL/CIN-1)

Low-grade cervical lesions are defined by early changes in size, shape, and number of abnormal cells formed on the surface of the cervix and may be referred to as mild dysplasia, LSIL, or CIN-1.

High-grade cervical lesions (HSIL/ CIN-2 / CIN-3 / CIS)

High-grade cervical lesions are defined by a large number of precancerous cells on the surface of the cervix that are distinctly different from normal cells. They have the potential to become cancerous cells and invade deeper tissues of the cervix. These lesions may be referred to as moderate or severe dysplasia, HSIL, CIN-2, CIN-3, or cervical carcinoma in situ (CIS).

Carcinoma in situ (CIS)

Cancerous cells are confined to the cervix and have not spread to other parts of the body.

Invasive cervical cancer (ICC) / Cervical cancer

If the high-grade precancerous cells invade deeper tissues of the cervix or to other tissues or organs, then the disease is called invasive cervical cancer or cervical cancer.

Invasive squamous cell carcinoma

Invasive carcinoma composed of cells resembling those of squamous epithelium.

Adenocarcinoma

Invasive tumour with glandular and squamous elements intermingled.

4.1.2 HPV prevalence in women with normal cytology

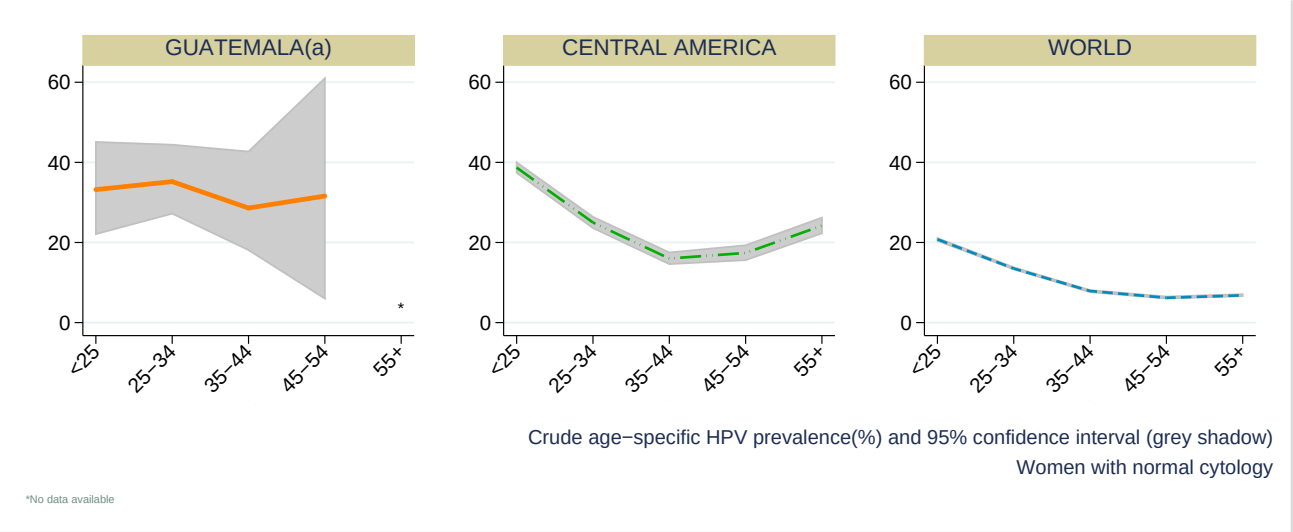
Table 14: Prevalence of HPV among women with normal cytology

Country/Region	Number of women tested	HPV prevalence %	(95% CI)
Guatemala[a]	274	33.2	(27.7-39.1)
Central America	24783	20.6	(20.1-21.1)
World	436430	11.4	(11.3-11.5)

Data sources:
Data have been compiled by the HPV Information Centre in the Unit of Infections and Cancer at the Institut Catala d'Oncologia and have been published as meta-analysis in: De Sanjosé S, Lancet Infect Dis 2007; 7: 453 and Bruni L, 25th IPV Society Meeting, Malmo, Sweden, 8-14 May 2009 (Manuscript in preparation).
[a] Valles X, Int J Cancer 2009; :

For Central America and the World, refer to specific reports or methods document for complete data sources.

Figure 24: Crude age-specific HPV prevalence in women with normal cytology in Guatemala compared to Central America and the World.



Data sources:
Data have been compiled by the HPV Information Centre in the Unit of Infections and Cancer at the Institut Catala d'Oncologia and have been published as meta-analysis in: De Sanjosé S, Lancet Infect Dis 2007; 7: 453 and Bruni L, 25th IPV Society Meeting, Malmo, Sweden, 8-14 May 2009 (Manuscript in preparation).
[a] Valles X, Int J Cancer 2009; :

For Central America and the World, refer to specific reports or methods document for complete data sources.

4.1.3 HPV type distribution among women with normal cytology, precancerous cervical lesions and cervical cancer

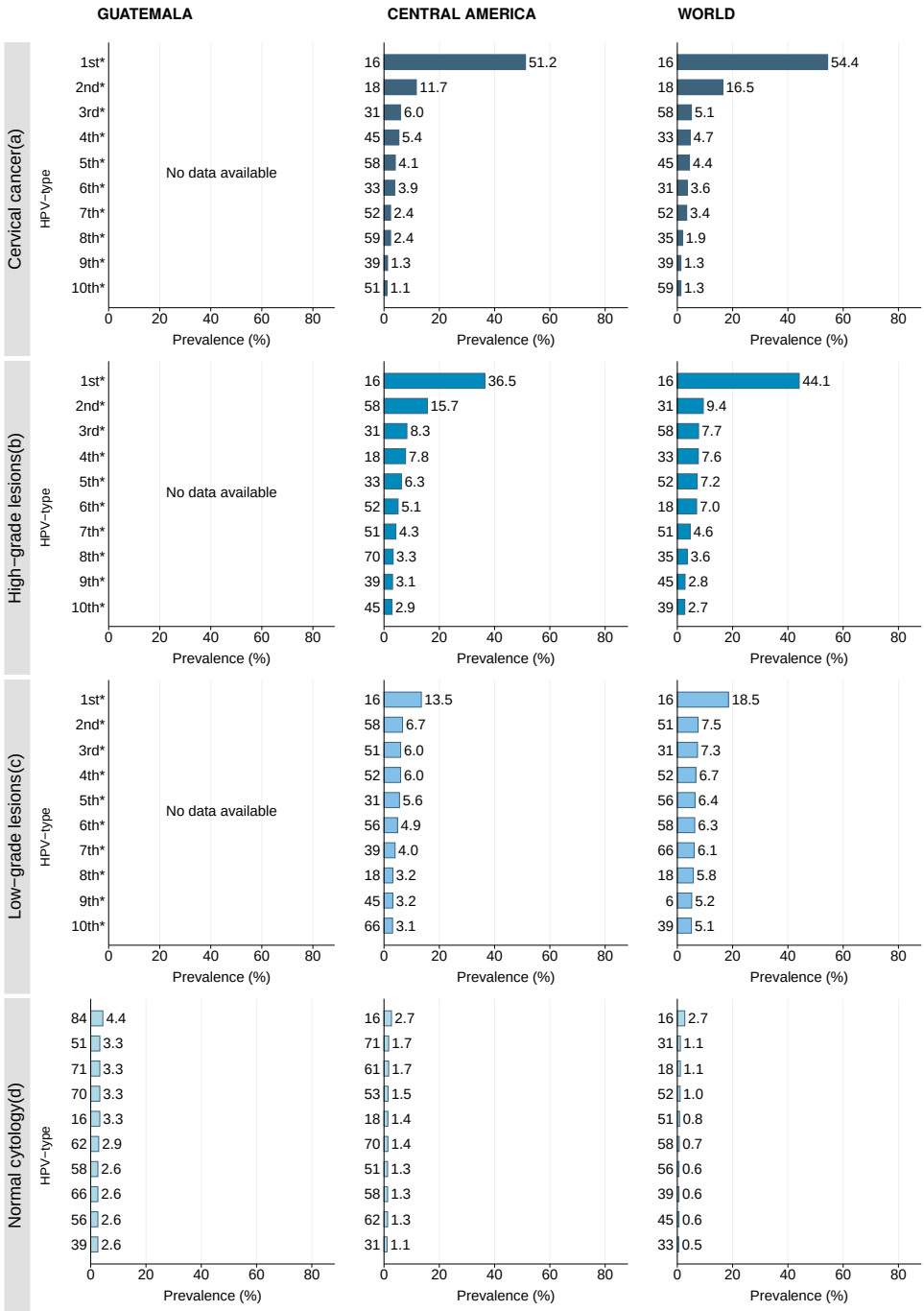
Table 15: Prevalence of HPV-16 and HPV-18 by cytology in Guatemala, Central America and the World

	Guatemala		Central America		World	
	No. tested	HPV 16/18 Prevalence % (95% CI)	No. tested	HPV 16/18 Prevalence % (95%CI)	No. tested	HPV 16/18 Prevalence % (95%CI)
Normal cytology[a]	-	- -	12381	4.1 (3.8-4.5)	218339	3.8 (3.7-3.9)
Low-grade lesions†[b]	-	- -	571	16.7 (13.7-20.0)	14762	24.3 (23.6-25.0)
High-grade lesions‡[c]	-	- -	447	44.3 (39.6-49.0)	14901	51.1 (50.3-51.9)
Cervical cancer[d]	-	- -	463	62.9 (58.3-67.3)	22826	70.9 (70.3-71.5)

The samples for HPV testing come from cervical specimens (fresh / fixed biopsies or exfoliated cells).
Abbreviations used:
95% CI: 95% Confidence Interval
†Low-grade lesions: LSIL or CIN-1
‡High-grade lesions: CIN-2, CIN-3, CIS or HSIL
Data sources:
[a] Data have been compiled by the HPV Information Centre in the Unit of Infections and Cancer at the Institut Catala d'Oncologia and have been published as meta-analysis in: De Sanjosé S, Lancet Infect Dis 2007; 7: 453 and Bruni L, 25th IPV Society Meeting, Malmo, Sweden, 8-14 May 2009 (Manuscript in preparation).
Specific for Guatemala: Valles X, Int J Cancer 2009; :
[b] Data have been compiled by the IARC Infection and Cancer Epidemiology Group and have been published as a systematic review and meta-analysis in: Clifford GM, Cancer Epidemiol Biomarkers Prev 2005; 14: 1157
[c] Data have been compiled by the IARC Infection and Cancer Epidemiology Group and have been published as a systematic review and meta-analysis in: Clifford G, Br J Cancer 2003;89:101 | Smith JS Int J Cancer 2007;121:621
[d] Data have been compiled by the IARC Infection and Cancer Epidemiology Group and have been published as a systematic review and meta-analysis in: Clifford G, Br J Cancer 2003;88:63 | Clifford G, Int J Cancer 2008; 122: 1684

For Central America and the World, refer to specific reports or methods document for complete data sources.

Figure 25: Ten most frequent HPV types among women with and without cervical lesions in Guatemala compared to Central America and the World



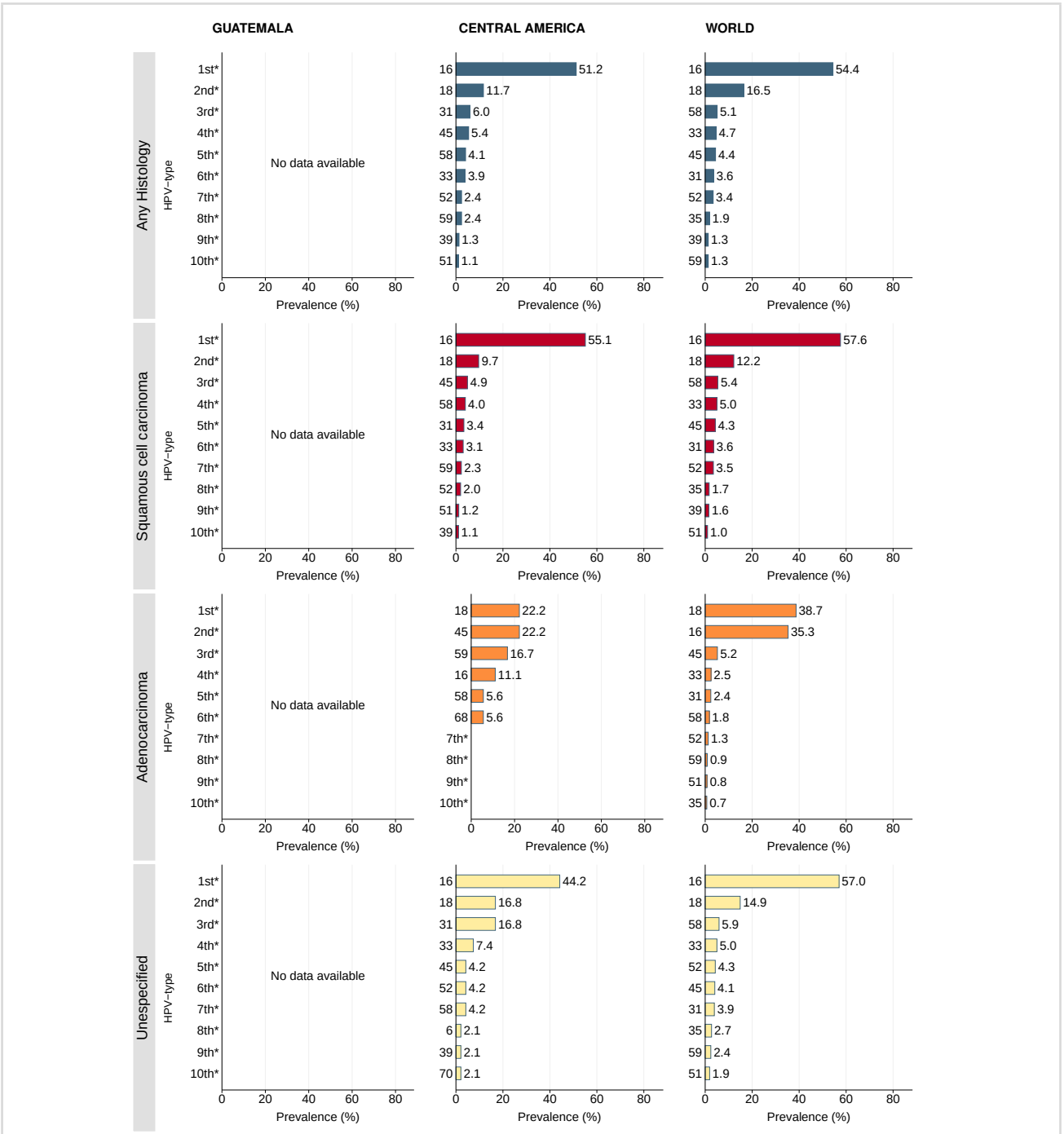
The samples for HPV testing come from cervical specimens (fresh / fixed biopsies or exfoliated cells).
∗No data available. No more types than shown were tested or were positive

The ranking of the ten most frequent HPV types may present less than ten types because only a limited number of types were tested or were HPV-positive.

Data sources:
[a] Data have been compiled by the IARC Infection and Cancer Epidemiology Group and have been published as a systematic review and meta-analysis in: Clifford G, Br J Cancer 2003;88:63 | Clifford G, Int J Cancer 2008; 122: 1684
[b] Data have been compiled by the IARC Infection and Cancer Epidemiology Group and have been published as a systematic review and meta-analysis in: Clifford G, Br J Cancer 2003;89:101 | Smith JS Int J Cancer 2007;121:621
[c] Data have been compiled by the IARC Infection and Cancer Epidemiology Group and have been published as a systematic review and meta-analysis in: Clifford GM, Cancer Epidemiol Biomarkers Prev 2005; 14: 1157
[d] Data have been compiled by the HPV Information Centre in the Unit of Infections and Cancer at the Institut Catala d'Oncologia and have been published as meta-analysis in: De Sanjosé S, Lancet Infect Dis 2007; 7: 453 and Bruni L, 25th IPV Society Meeting, Malmo, Sweden, 8-14 May 2009 (Manuscript in preparation).
Specific for Guatemala: Valles X, Int J Cancer 2009; :

For Central America and the World, refer to specific reports or methods document for complete data sources.

Figure 26: Ten most frequent HPV types among women with invasive cervical cancer in Guatemala compared to Central America and the World, by histology



The samples for HPV testing come from cervical specimens (fresh / fixed biopsies or exfoliated cells).
∗No data available. No more types than shown were tested or were positive

The ranking of the ten most frequent HPV types may present less than ten types because only a limited number of types were tested or were HPV-positive.
Data sources:
Data have been compiled by the IARC Infection and Cancer Epidemiology Group and have been published as a systematic review and meta-analysis in: Clifford G, Br J Cancer 2003;88:63 | Clifford G, Int J Cancer 2008; 122: 1684
For Central America and the World, refer to specific reports or methods document for complete data sources.

Table 16: Type-specific HPV prevalence in women with normal cytology, precancerous cervical lesions and invasive cervical cancer in Guatemala

HPV Type	Normal cytology[a] No. tested	HPV Prev % (95%CI)	Low-grade lesions†[b] No. tested	HPV Prev % (95%CI)	High-grade lesions‡[c] No. tested	HPV Prev % (95%CI)	Cervical cancer[d] No. tested	HPV Prev % (95%CI)
6	274	1.1 (0.2-3.2)	-	- -	-	- -	-	- -
11	274	0.0 (0.0-1.3)	-	- -	-	- -	-	- -
13	-	- -	-	- -	-	- -	-	- -
16	274	3.3 (1.5-6.1)	-	- -	-	- -	-	- -
18	274	2.2 (0.8-4.7)	-	- -	-	- -	-	- -
26	274	0.0 (0.0-1.3)	-	- -	-	- -	-	- -
30	-	- -	-	- -	-	- -	-	- -
31	274	0.0 (0.0-1.3)	-	- -	-	- -	-	- -
32	-	- -	-	- -	-	- -	-	- -
33	274	0.0 (0.0-1.3)	-	- -	-	- -	-	- -
34	274	0.0 (0.0-1.3)	-	- -	-	- -	-	- -
35	274	0.7 (0.1-2.6)	-	- -	-	- -	-	- -
39	274	2.6 (1.0-5.2)	-	- -	-	- -	-	- -
40	274	0.0 (0.0-1.3)	-	- -	-	- -	-	- -
42	274	0.0 (0.0-1.3)	-	- -	-	- -	-	- -
43	-	- -	-	- -	-	- -	-	- -
44	274	0.7 (0.1-2.6)	-	- -	-	- -	-	- -
45	274	1.5 (0.4-3.7)	-	- -	-	- -	-	- -
51	274	3.3 (1.5-6.1)	-	- -	-	- -	-	- -
52	274	2.6 (1.0-5.2)	-	- -	-	- -	-	- -
53	274	1.1 (0.2-3.2)	-	- -	-	- -	-	- -
54	274	1.1 (0.2-3.2)	-	- -	-	- -	-	- -
55	-	- -	-	- -	-	- -	-	- -
56	274	2.6 (1.0-5.2)	-	- -	-	- -	-	- -
57	-	- -	-	- -	-	- -	-	- -
58	274	2.6 (1.0-5.2)	-	- -	-	- -	-	- -
59	274	0.7 (0.1-2.6)	-	- -	-	- -	-	- -
61	274	1.1 (0.2-3.2)	-	- -	-	- -	-	- -
62	274	2.9 (1.3-5.7)	-	- -	-	- -	-	- -
64	-	- -	-	- -	-	- -	-	- -
66	274	2.6 (1.0-5.2)	-	- -	-	- -	-	- -
67	274	0.0 (0.0-1.3)	-	- -	-	- -	-	- -
68	274	0.4 (0.0-2.0)	-	- -	-	- -	-	- -
69	274	0.4 (0.0-2.0)	-	- -	-	- -	-	- -
70	274	3.3 (1.5-6.1)	-	- -	-	- -	-	- -
71	274	3.3 (1.5-6.1)	-	- -	-	- -	-	- -
72	274	1.8 (0.6-4.2)	-	- -	-	- -	-	- -
73	274	0.0 (0.0-1.3)	-	- -	-	- -	-	- -
74	-	- -	-	- -	-	- -	-	- -
81	274	1.5 (0.4-3.7)	-	- -	-	- -	-	- -
82	274	1.1 (0.2-3.2)	-	- -	-	- -	-	- -
83	274	2.2 (0.8-4.7)	-	- -	-	- -	-	- -
84	274	4.4 (2.3-7.5)	-	- -	-	- -	-	- -
85	-	- -	-	- -	-	- -	-	- -
86	-	- -	-	- -	-	- -	-	- -
89	274	0.4 (0.0-2.0)	-	- -	-	- -	-	- -
90	-	- -	-	- -	-	- -	-	- -
91	-	- -	-	- -	-	- -	-	- -

The samples for HPV testing come from cervical specimens (fresh / fixed biopsies or exfoliated cells).
Abbreviations used:
95% CI: 95% Confidence Interval
†Low-grade lesions: LSIL or CIN-1
‡High-grade lesions: CIN-2, CIN-3, CIS or HSIL
Data sources:
[a] Data have been compiled by the HPV Information Centre in the Unit of Infections and Cancer at the Institut Catala d'Oncologia and have been published as meta-analysis in: De Sanjosé S, Lancet Infect Dis 2007; 7: 453 and Bruni L, 25th IPV Society Meeting, Malmo, Sweden, 8-14 May 2009 (Manuscript in preparation).
Valles X, Int J Cancer 2009; :
[b] Data have been compiled by the IARC Infection and Cancer Epidemiology Group and have been published as a systematic review and meta-analysis in: Clifford GM, Cancer Epidemiol Biomarkers Prev 2005; 14: 1157
[c] Data have been compiled by the IARC Infection and Cancer Epidemiology Group and have been published as a systematic review and meta-analysis in: Clifford G, Br J Cancer 2003;89:101 | Smith JS Int J Cancer 2007;121:621
[d] Data have been compiled by the IARC Infection and Cancer Epidemiology Group and have been published as a systematic review and meta-analysis in: Clifford G, Br J Cancer 2003;88:63 | Clifford G, Int J Cancer 2008; 122: 1684

Table 17: Type-specific HPV prevalence among invasive cervical cancer cases in Guatemala, by histology

HPV Type	Any Histology		Squamous cell carcinoma		Adenocarcinoma		Unespecified	
	No. tested	HPV Prev % (95%CI)	No. tested	HPV Prev % (95%CI)	No. tested	HPV Prev % (95%CI)	No. tested	HPV Prev % (95%CI)
6	-	- -	-	- -	-	- -	-	- -
11	-	- -	-	- -	-	- -	-	- -
16	-	- -	-	- -	-	- -	-	- -
18	-	- -	-	- -	-	- -	-	- -
31	-	- -	-	- -	-	- -	-	- -
33	-	- -	-	- -	-	- -	-	- -
35	-	- -	-	- -	-	- -	-	- -
39	-	- -	-	- -	-	- -	-	- -
45	-	- -	-	- -	-	- -	-	- -
51	-	- -	-	- -	-	- -	-	- -
52	-	- -	-	- -	-	- -	-	- -
56	-	- -	-	- -	-	- -	-	- -
58	-	- -	-	- -	-	- -	-	- -
59	-	- -	-	- -	-	- -	-	- -
66	-	- -	-	- -	-	- -	-	- -
68	-	- -	-	- -	-	- -	-	- -
70	-	- -	-	- -	-	- -	-	- -
73	-	- -	-	- -	-	- -	-	- -
82	-	- -	-	- -	-	- -	-	- -

The samples for HPV testing come from cervical specimens (fresh / fixed biopsies or exfoliated cells).
Abbreviations used:
95% CI: 95% Confidence Interval

Data sources:
Data have been compiled by the IARC Infection and Cancer Epidemiology Group and have been published as a systematic review and meta-analysis in: Clifford G, Br J Cancer 2003;88:63 | Clifford G, Int J Cancer 2008; 122: 1684

4.2 HPV burden in anogenital cancers other than the cervix

4.2.1 Anal cancer

Anal cancer is similar to cervical cancer with respect to overall HPV DNA positivity, with approximately 85% of cases associated with HPV infection worldwide. HPV-16 is the most common detected type, representing 87% of all HPV-positive tumours. HPV-18 is the second most common type detected and is found in approximately 9% of cases. HPV DNA is also detected in the majority of precancerous anal lesions (AIN) and the prevalence of HPV increases with the severity of the lesion, 75% in AIN1, 86% in AIN2, and 94% in AIN3. In this section, the burden of HPV among cases of anal cancers in Guatemala is presented.
(*Vaccine 2006, Vol. 24, Supl 3; Vaccine 2008, Vol. 26, Supl 10; IARC Monographs 2007, Vol. 90*)

Table 18: Studies on HPV prevalence among cases of anal cancer in Guatemala

Study	HPV detection method	No. tested	HPV prevalence % (95% CI)	
No data available	-	-	-	-

Data sources:
Ongoing data are compiled by the HPV Information Centre in the Unit of Infections and Cancer at the Institut Catala d'Oncologia based on the initial meta-analysis conducted by the IARC Infection and Cancer Epidemiology Group in: De Vuyst H, Int J Cancer 2009; 124: 1626.

Table 19: Pooled estimate of HPV prevalence among cases of anal cancer by sex in Guatemala

Sex	No. tested	HPV prevalence % (95% CI)
Female	-	- -
Male	-	- -
Unespecified	-	- -

Data sources:
Ongoing data are compiled by the HPV Information Centre in the Unit of Infections and Cancer at the Institut Catala d'Oncologia based on the initial meta-analysis conducted by the IARC Infection and Cancer Epidemiology Group in: De Vuyst H, Int J Cancer 2009; 124: 1626.

Table 20: Pooled estimate of HPV prevalence among men who have sex with men (MSM) and non-MSM with anal cancer in Guatemala

MSM	No. tested	HPV prevalence % (95% CI)
MSM	-	- -
Non-MSM	-	- -
Unespecified	-	- -

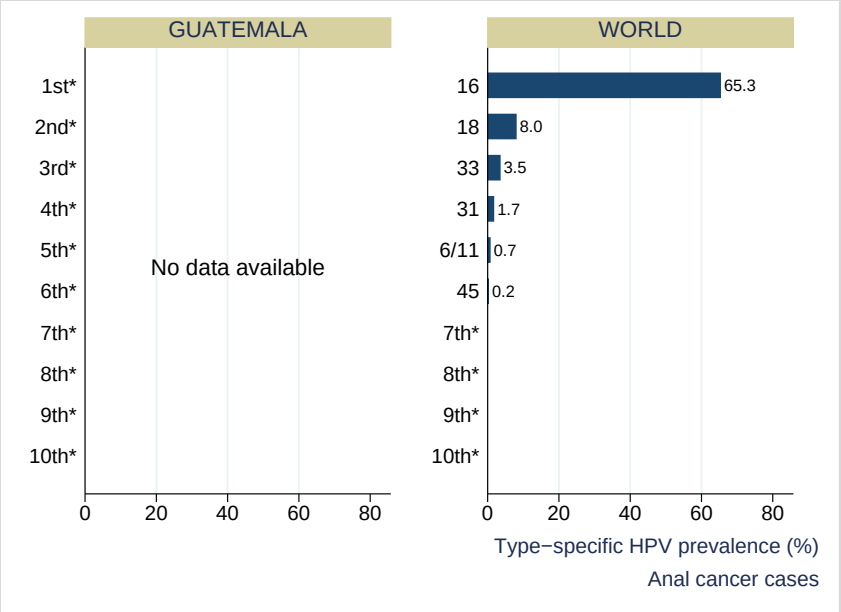
Data sources:
Ongoing data are compiled by the HPV Information Centre in the Unit of Infections and Cancer at the Institut Catala d'Oncologia based on the initial meta-analysis conducted by the IARC Infection and Cancer Epidemiology Group in: De Vuyst H, Int J Cancer 2009; 124: 1626.

Table 21: Pooled estimate of HPV prevalence among cases of anal cancer by histology in Guatemala

Histology	No. tested	HPV prevalence % (95% CI)
Any Histology	-	- -
Basaloid/Cloacogenic SCC	-	- -
Keratinizing SCC	-	- -
Unespecified SCC	-	- -
Adenocarcinoma	-	- -
Others	-	- -

Data sources:
Ongoing data are compiled by the HPV Information Centre in the Unit of Infections and Cancer at the Institut Catala d'Oncologia based on the initial meta-analysis conducted by the IARC Infection and Cancer Epidemiology Group in: De Vuyst H, Int J Cancer 2009; 124: 1626.

Figure 27: Ten most frequent HPV types among cases of anal cancer in Guatemala compared to the World



∗Not available. No more types than shown were tested or were positive

Data sources:

Ongoing data are compiled by the HPV Information Centre in the Unit of Infections and Cancer at the Institut Catala d'Oncologia based on the initial meta-analysis conducted by the IARC Infection and Cancer Epidemiology Group in: De Vuyst H, Int J Cancer 2009; 124: 1626.

World: Refer to specific World report or methods document for data sources

4.2.2 Vulvar cancer

Vulvar cancer has two distinct histological patterns with two different risk factor profiles: (1) basaloid/warty types (2) keratanizing types. The majority of vulvar carcinomas are of the basaloid warty type (>55%), which occur mainly in younger women compared to the keratanizing types, and are associated with similar risk factors for HPV infection in the cervix. In contrast, keratanizing vulvar carcinomas are associated with a low prevalence of HPV DNA (<=10%) that occur mainly in older women and are associated with lichen planus. In a case series, HPV DNA prevalence ranged from 72-100% among cases of high-grade vulvar neoplasias (VIN3) and 27.3-100% among vulvar carcinomas (3.9-6.3% in keratinzing types). Similarly, a meta-analysis estimated a HPV prevalence of 76% for VIN and 36% for vulvar carcinomas. HPV-16 is the most common detected type (65-93% in VIN and 71% for vulvar cancer) followed by HPV-18. In this section, the HPV burden among cases of vulvar cancers in Guatemala is presented.
(*Vaccine 2006, Vol. 24, Supl 3; Vaccine 2008, Vol. 26, Supl 10; IARC Monographs 2007, Vol. 90*)

Table 22: Studies on HPV prevalence among cases of vulvar cancer in Guatemala

Study	HPV detection method	No. tested	HPV prevalence % (95% CI)
No data available	-	-	- -

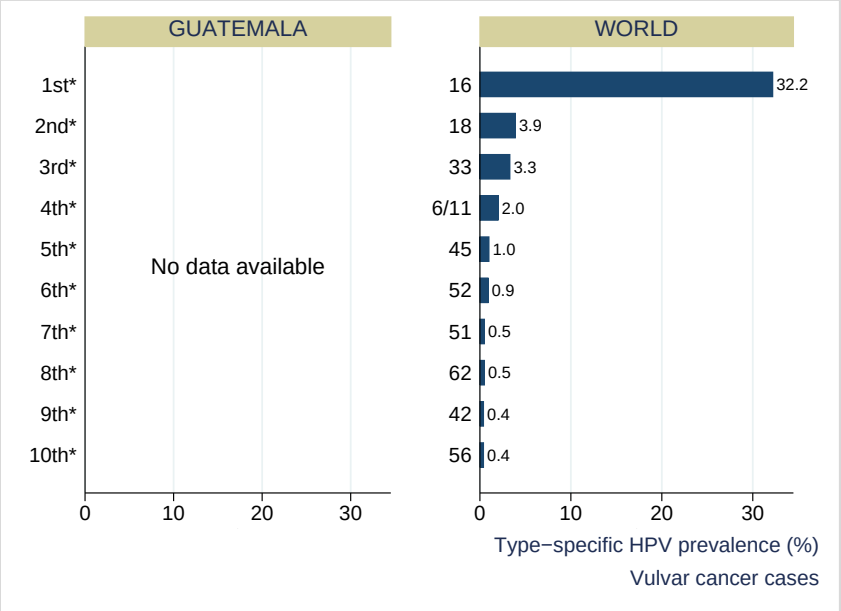
Data sources:
Ongoing data are compiled by the HPV Information Centre in the Unit of Infections and Cancer at the Institut Catala d'Oncologia based on the initial meta-analysis conducted by the IARC Infection and Cancer Epidemiology Group in: De Vuyst H, Int J Cancer 2009; 124: 1626.

Table 23: Pooled estimate of HPV prevalence among cases of vulvar cancer by histology in Guatemala

Histology	No. tested	HPV prevalence % (95% CI)
Any Histology	-	- -
Warty-Basaloid SCC	-	- -
Keratinizing SCC	-	- -
Verrucous SCC	-	- -
Unespecified SCC	-	- -
Adenocarcinoma	-	- -

Data sources:
Ongoing data are compiled by the HPV Information Centre in the Unit of Infections and Cancer at the Institut Catala d'Oncologia based on the initial meta-analysis conducted by the IARC Infection and Cancer Epidemiology Group in: De Vuyst H, Int J Cancer 2009; 124: 1626.

Figure 28: Ten most frequent HPV types among cases of vulvar cancer in Guatemala compared to the World



∗Not available. No more types than shown were tested or were positive
Data sources:
Ongoing data are compiled by the HPV Information Centre in the Unit of Infections and Cancer at the Institut Catala d'Oncologia based on the initial meta-analysis conducted by the IARC Infection and Cancer Epidemiology Group in: De Vuyst H, Int J Cancer 2009; 124: 1626.
World: Refer to specific World report or methods document for data sources

4.2.3 Vaginal cancer

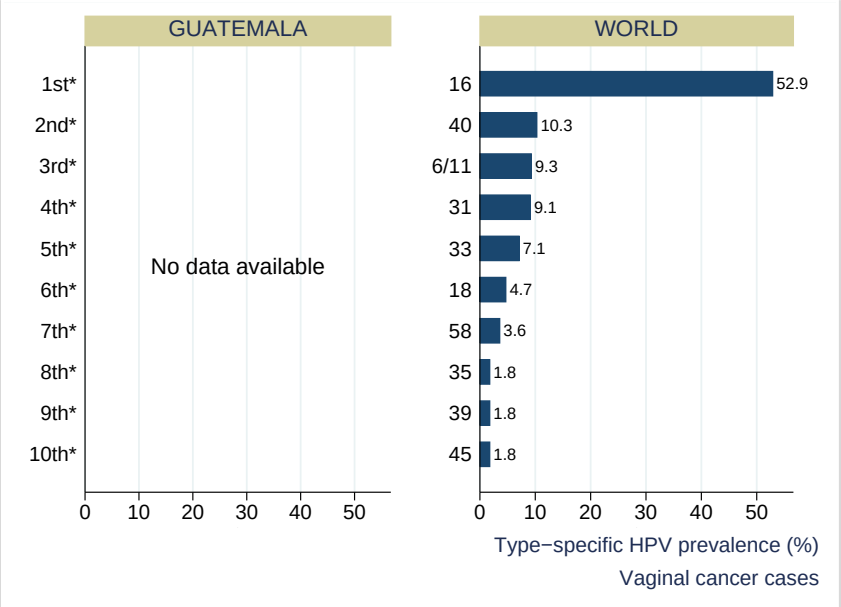
Vaginal and cervical cancers share similar risk factors and it is generally accepted that both carcinomas share the same aetiology of HPV infection although there is limited evidence available. Women with vaginal cancer are more likely to have a history of other ano-genital cancers, particularly of the cervix, and these two carcinomas are frequently diagnosed simultaneously. HPV DNA is detected among 91% of invasive vaginal carcinomas and 82% of high-grade vaginal neoplasias (VAIN3).In a case series of vaginal cancers, HPV-16 is the most common type in at least 70% of HPV-positive carcinomas. In this section, the HPV burden among cases of vaginal cancers in Guatemala is presented.
(*Vaccine 2006, Vol. 24, Supl 3; Vaccine 2008, Vol. 26, Supl 10; IARC Monographs 2007, Vol. 90*)

Table 24: Studies on HPV prevalence among cases of vaginal cancer in Guatemala

Study	HPV detection method	Histology	No. tested	HPV prevalence % (95% CI)
No data available	-	-	-	- -

Data sources:
Ongoing data are compiled by the HPV Information Centre in the Unit of Infections and Cancer at the Institut Catala d'Oncologia based on the initial meta-analysis conducted by the IARC Infection and Cancer Epidemiology Group in: De Vuyst H, Int J Cancer 2009; 124: 1626.

Figure 29: Ten most frequent HPV types among vaginal cancer cases in Guatemala compared to the World



∗Not available. No more types than shown were tested or were positive
Data sources:
Ongoing data are compiled by the HPV Information Centre in the Unit of Infections and Cancer at the Institut Catala d'Oncologia based on the initial meta-analysis conducted by the IARC Infection and Cancer Epidemiology Group in: De Vuyst H, Int J Cancer 2009; 124: 1626.
World: Refer to specific World report or methods document for data sources

4.2.4 Penile cancer

The geographical correlation between the incidence of penile and cervical cancers and the concordance of these two cancers among married couples suggested the common aetiology of HPV infection. HPV DNA is detectable in approximately 40-50% of all penile cancers. HPV DNA is detectable among penile intraepithelial neoplasias with the basoloid histological type, ranging from 75-80% of cases, and decreasing to 30-60% among invasive squamous cell carcinomas (SCC). The majority of penile carcinomas are squamous cell carcinomas (SCC), and it has been observed that some cases of penile SCC are HPV DNA negative. HPV DNA positvity among penile cancers varies with histopathological type, with a prevalence of 47% in basaloid/warty types, 75% in purely basaloid types, and 11% in keratinizing SCC. Among HPV-DNA positive cases, HPV-16 is the most common type. In this section, the HPV burden among cases of penile cancers in Guatemala is presented. (*Vaccine 2006, Vol. 24, Supl 3; Vaccine 2008, Vol. 26, Supl 10; IARC Monographs 2007, Vol. 90*)

Table 25: Studies on HPV prevalence among cases of penile cancer in Guatemala

Study	HPV detection method	No. tested	HPV prevalence % (95% CI)
No data available	-	-	- -

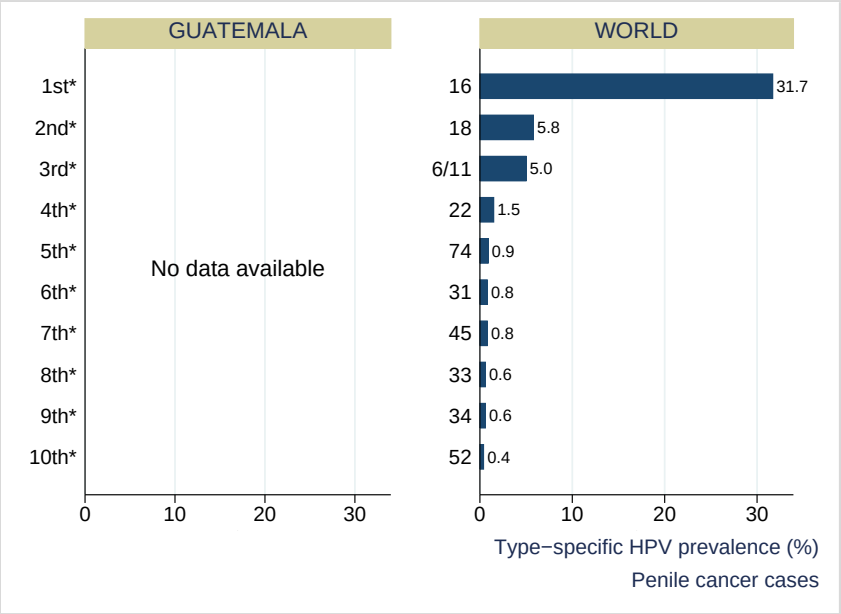
Data sources:
Data have been compiled by the HPV Information Centre in the Unit of Infections and Cancer at the Institut Catala d'Oncologia and have been published as systematic review in: Miralles-Guri C, J Clin Pathol 2009; In press

Table 26: Pooled estimate of HPV prevalence among cases of penile cancer by histology in Guatemala

Histology	No. tested	HPV prevalence % (95% CI)
Any Histology	-	- -
Carc. In situ	-	- -
Basaloid SCC	-	- -
Keratinizing SCC	-	- -
SCC (unspecified)	-	- -
Non-keratinizing SCC	-	- -
Warty SCC	-	- -
Verrucous SCC	-	- -

Data sources:
Data have been compiled by the HPV Information Centre in the Unit of Infections and Cancer at the Institut Catala d'Oncologia and have been published as systematic review in: Miralles-Guri C, J Clin Pathol 2009; In press

Figure 30: Ten most frequent HPV types among cases of penile cancer in Guatemala compared to the World



∗Not available. No more types than shown were tested or were positive
Data sources:
Data have been compiled by the HPV Information Centre in the Unit of Infections and Cancer at the Institut Catala d'Oncologia and have been published as systematic review in: Miralles-Guri C, J Clin Pathol 2009; In press
World: Refer to specific World report or methods document for data sources

4.3 HPV burden in men

The information to date regarding penile HPV infection is primarily derived from studies that examined husbands of female cervical cancer cases, cross-sectional studies of selected populations such as individuals with sexually transmitted infections (STI) and military recruits, as well as from small prospective studies. HPV infection in the genital tract has been detected in up to 73% of healthy men. Like other STIs, HPV may be transmitted more readily from men to women than from women to men. In this section, the HPV burden among men in Guatemala is presented.

(*Vaccine 2008, Vol. 26, Supl 10*)

Table 27: Studies on HPV prevalence among men in Guatemala

Study	Anatomic sites samples	HPV detection method	Population	Age (years)	HPV prevalence		
					Men tested	%	(95% CI)
No data available	-	-	-	-	-	-	-

Table 28: Studies on high-risk HPV Prevalence among men in Guatemala

Study	Anatomic sites samples	High-risk HPV tested	Population	Age (years)	HPV prevalence		
					Men tested	%	(95% CI)
No data available	-	-	-	-	-	-	-

5 Factors contributing to cervical cancer

HPV is a necessary cause of cervical cancer, but it is not a sufficient cause. Other cofactors are necessary for progression from cervical HPV infection to cancer. Tobacco smoking, high parity, long-term hormonal contraceptive use, and co-infection with HIV have been identified as established cofactors. Co-infection with Chlamydia trachomatis and herpes simplex virus type-2, immunosuppression, and certain dietary deficiencies are other probable cofactors. Genetic and immunological host factors and viral factors other than type, such as variants of type, viral load and viral integration, are likely to be important but have not been clearly identified. (*Muñoz N, Vaccine 2006; 24S3: S3-1*)

In this section, the prevalence of smoking, parity (fertility), oral contraceptive use, and HIV in Guatemala are presented.

Table 29: Factors contributing to cervical carcinogenesis (cofactors) in Guatemala

INDICATOR		MALE	FEMALE	TOTAL
Smoking[1]				
Smoking of any tobacco prevalence (%)	Current	24.8[a]	3.9[a]	-
	Daily	7.8[a]	0.8[a]	-
Cigarette smoking prevalence (%)	Current	24.8[a]	3.9[a]	-
	Daily	7.8[a]	0.8[a]	-
Parity[2,3]				
Total fertility rate per woman		-	4.5[b]	-
Age-specific fertility rate (per 1000 women)	15-19 yrs	-	120[b]	-
	20-24 yrs	-	235[b]	-
	25-29 yrs	-	216[b]	-
	30-34 yrs	-	158[b]	-
	35-39 yrs	-	121[b]	-
	40-44 yrs	-	44[b]	-
	44-49 yrs	-	7[b]	-
Hormonal contraception[4]				
Oral contraceptive use (%)		-	-	3.4[c]
HIV				
Adult (15-49 yrs) prevalence percent [low estimate - high estimate][5]		-	-	0.8 [0.5-1.1][d]
Young adults (15-24 yrs) rate of HIV (%) [low estimate - high estimate][5]		-	1.5 [0.6-2.4][d]	-
Estimated number of adults and children living with HIV [low estimate - high estimate][5]		-	-	59000 [41000-84000][d]
Estimated number of adults (15+ yrs) living with HIV [low estimate - high estimate][5]		-	52000 [35000-76000][d]	53000 [35000-77000][d]
Estimated number of AIDS deaths in adults and children [low estimate - high estimate][5]		-	-	3900 [2500-5500][d]
Estimated antiretroviral therapy coverage (%) [low estimate - high estimate][6,7]		-	-	37% (28%-51%)[d]
Estimated number of people receiving antiretroviral therapy [low estimate - high estimate][6,7]		-	-	7800 (7400-8200)[d]
HIV prevalence (%) among female sex workers in the capital city[5]		-	-	-
HIV prevalence (%) among men who have sex with men in the capital city[5]		-	-	-

Year of estimation: [a] 2008; [b] 2000; [c] 2002; [d] 2007;
[2] Fertility rate is a proxy measure of parity.
[6] The coverage estimates are based on the estimated unrounded numbers of people receiving antiretroviral therapy and the estimated unrounded need for antiretroviral therapy (based on UNAIDS/WHO methodology). The ranges in coverage estimates are based on plausibility bounds in the denominator: that is, low and high estimates of need.
Data sources:
[1] WHO Report on the Global Tobacco Epidemic, 2008 - The MPOWER package. Tobacco Free Initiative, World Health Organization, 2008 (http://www.who.int/tobacco/mpower/gtcr_download/en/index.html)
[3] World fertility patterns 2007 [wall chart]. New York, Population Division, Department of Economic and Social Affairs, United Nations Secretariat, 2008.
[4] United Nations, Department of Economic and Social Affairs, Population Division. World Contraceptive Use 2005 (http://www.un.org/esa/population/publications/contraceptive2005/WCU2005.htm)
[5] 2008 Report on the global AIDS epidemic, UNAIDS/WHO, July 2008.
[7] World Health Organization. WHO and HIV/AIDS. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector: progress report 2008.

6 Sexual and reproductive health behaviour indicators

Sexual intercourse is the primary route of transmission of genital HPV infection. Information about sexual and reproductive health behaviours is essential to the design of effective preventive strategies against anogenital cancers. In this section, we describe sexual and reproductive health indicators that may be used as proxy measures of risk for HPV infection and anogenital cancers.

Table 30: Time of sexual intercourse and high-risk sexual behaviour in Guatemala, for females and males

Indicator	Male	Female
Time of sexual intercourse		
Median age at first sex among young men and women (15-24 years)[1]	-	19.3[a]
Median age at first sexual intercourse among men (25-54 years) and women (25-49 years)[2]	-	18.3[b]
% of young people (15-24 years) who have had sex before the age of 15	-	-
Abstinence of never-married young men and women (age 15-24 years)	-	-
High-risk sexual behaviour		
Extramarital sex in the last year	-	-
Multiple partners in the last year among sexually active respondents aged 15-49	-	-
Commercial sex in last year	-	-

Year of estimation: [a] 1987; [b] 1998-1999;
Data sources:
[1] Encuesta Nacional de Salud Meterno Infantil 1987, Guatemala
[2] Guatemala Encuesta Nacional de Salud Materno Infantil

Table 31: Reproductive health indicators in Guatemala

Factor	Indicator		Male	Female	Total
Age at first marriage[1]	Average age at first marriage:		23.8[a]	21.3[a]	-
	Percentage of ever married	15-19 yrs	7.8[a]	24.2[a]	-
		20-24 yrs	45.9[a]	66.8[a]	-
		45-49 yrs	95.0[a]	96.6[a]	-
	Difference in average at first marriage between men and women		-	-	2.5[a]
Married or in union[2]	Women aged 15-49 married or in union (thousands)		-	2120[b]	-
Contraceptive use[3]	Any contraceptive method (%)		-	43.3[b]	-
	Annual change (1997 to 2007): any contraceptive method		-	1.7[b]	-
	Annual change (1997 to 2007): modern methods		-	1.1[b]	-
	Modern methods	Condom (%)	-	2.3[b]	-
		IUD (%)	-	1.9[b]	-
		Injectable or implant (%)	-	9.1[b]	-
		Pill/Oral contraceptive (%)	-	3.4[b]	-
		Sterilization (%)	1.0[b]	16.8[b]	-
		Vaginal barrier method (%)	-	0.1[b]	-
		Other modern methods (%)	-	0.0[b]	-
		Prevalence of modern methods (%)	-	34.4[b]	-
	Traditional methods	With-drawal (%)	-	2.3[b]	-
		Rhythm (%)	-	6.3[b]	-
		Other traditional methods (%)	-	0.2[b]	-

Year of estimation: [a] 1990; [b] 2002;
Data sources:
[1] World Bank HNPStats [online database]. Washington DC, World Bank Health, Nutrition and Population (HNP) statistics, 2007 (http://go.worldbank.org/N2N84RDV00, accessed 28 Jan 2009).
[2] United Nations, Department of Economic and Social Affairs, Population Division. World Contraceptive Use 2005 (http://www.un.org/esa/population/publications/contraceptive2005/WCU2005.htm)
[3] United Nations, Department of Economic and Social Affairs, Population Division. World Contraceptive Use 2005 (http://www.un.org/esa/population/publications/contraceptive2007/contraceptive2007.htm)

7 HPV preventive strategies

It is established that well-organised cervical screening programmes or widespread good quality cytology can reduce cervical cancer incidence and mortality. The introduction of HPV vaccination could also effectively reduce the burden of cervical cancer in the coming decades. In addition, male circumcision and the use of condoms have shown a significant protective effect against HPV transmission and may offer an alternative preventative strategy. This section presents indicators on basic characteristics and performance of cervical cancer screening, status of HPV vaccine licensure, introduction and country recommendations and the prevalence of male circumcision and condom use in Guatemala.

7.1 Cervical cancer screening practices

Table 32: Main characteristics of cervical cancer screening in Guatemala

Indicator	Value
Screening ages (years)	25-59
Screening interval (years) or frequency of screens	Annual for ages 30-45; Every 2 years for ages 30-59; Annual for ages 25-59
Lifetime number of recommended smears	15-34
Smear taker	-

Variable screening ages and screening intervals or frequency of screens depend on different guidelines followed in the country.
Data sources:
IARC Handbooks of Cancer Prevention Vol. 10: Cervix Cancer Screening. IARC Press. Lyon, 2005.

Table 33: Estimated coverage of cervical cancer screening in Guatemala

Reference	Year	Population studied	Rural or Urban	N Women	Age range	Coverage (%)	Within the last year(s)
ENSMI 2002[a]	2002	General female population	All	12119	15-49	42.7	Ever
Monteith 2005[b]	2002	General female population	All	9155	15-49	36.2	Ever
			Urban	-	15-49	48.0	Ever
			Rural	-	15-49	27.7	Ever

Notes and sources:
[a] Population-based nationwide household and individual survey. Sample of 12119 households with women aged 15-49 years.
Guatemala. Encuesta Nacional de Salud Materno Infantil 2002 (ENSMI). Instituto de Estadística de Guatemala (INE). 2002
[b] Data of from the DHS population-based survey on sexually active women aged 15-49.
Monteith RS, Stupp PW, McCracken SD. Reproductive, Maternal and Child Health in Central America. Trends and Challenges Facing Women and Children. El Salvador · Guatemala · Honduras · Nicaragua. Atlanta, GA, USA: Division of Reproductive Health, Centers for Disease Control and Prevention (DRH/CDC); 2005 Aug.

Figure 31: Estimated coverage of cervical cancer screening in Guatemala, by age and study

Table 34: Estimated coverage of cervical cancer screening in Guatemala, by region

Region	N women	Age range	Coverage (%)	LY*	Population	Reference
No data available	-	-	-	-	-	-

LY*: Within the last year(s)

7.2 HPV vaccination

7.2.1 HPV vaccine licensure and introduction

Table 35: Licensure status of current HPV vaccines in Guatemala

HPV vaccine	Date	Licensure
Bivalent vaccine/Cervarix	2009	Yes
Quadrivalent vaccine/Gardasil	2009	Yes

Due to importation, distribution, and other regulatory requirements, as well as price negotiations, a licensed vaccine may not necessarily be marketed in a given country.
Data sources:
Bivalent: GlaxoSmithKline Biologicals, Rixensart, Belgium, March 2009 | Quadrivalent: Merck & Co., Inc., Whitehouse Station, NJ, USA, March 2009

Table 36: HPV vaccine introduction in Guatemala

Indicator	Value
HPV vaccine schedule	-
Introduction in entire or part of the country	-
Comment	-

Data sources:
WHO-UNICEF Joint Reporting Form and WHO Regional offices 2009, WHO Immunization surveillance, assessment, and monitoring (http://www.who.int/immunization_monitoring/data/data_subject/en/index.html)

7.2.2 Country recommendations on the inclusion of HPV vaccines in national immunization programmes

Table 37: Summary of national HPV vaccine recommendations and programmatic aspects in Guatemala

Indicator	Date	Value
Finance mechanism	-	-
Delivery strategy	-	-
Integration of vaccination and cervical cancer screening program	-	-
Announcement date and type; and recommendation committee	-	-
Recommendation for primary target population	-	-
Recommendation for catch-up population	-	-
Recommendation for vaccinating males	-	-
Comments	-	-

7.3 Male circumcision and condom use

Table 38: Prevalence of male circumcision in Guatemala

Reference	Prevalence % (95%CI)	Method
WHO 2007	<20	Data from Demographic and Health Surveys (DHS) and other publications to categorize the country-wide prevalence of male circumcision as <20%, 20-80%, or >80%.
Drain 2006	<20	Data from Demographic and Health Surveys (DHS) and other publications to categorize the country-wide prevalence of male circumcision as <20%, 20-80%, or >80%.

Data sources:
Drain PK, BMC Infect Dis 2006; 6: 172 | WHO 2007: Male circumcision: Global trends and determinants of prevalence, safety and acceptability

Table 39: Prevalence of condom use in Guatemala

Indicator	Prevalence %	Year of estimation
Condom use	2.3	2002

Data sources:
United Nations, Department of Economic and Social Affairs, Population Division. World Contraceptive Use 2005 (http://www.un.org/esa/population/publications/contraceptive2007/contraceptive2007.htm)

8 Indicators related to immunzation practices other than HPV vaccines

This section presents data on immunization coverage and practices for selected vaccines. This information will be relevant for assessing the country's capacity to introduce and implement the new HPV vaccines. The data are periodically updated and posted on the WHO Immunization surveillance, assessment and monitoring website.
(http://www.who.int/immunization_monitoring/en/).

8.1 Immunization schedule

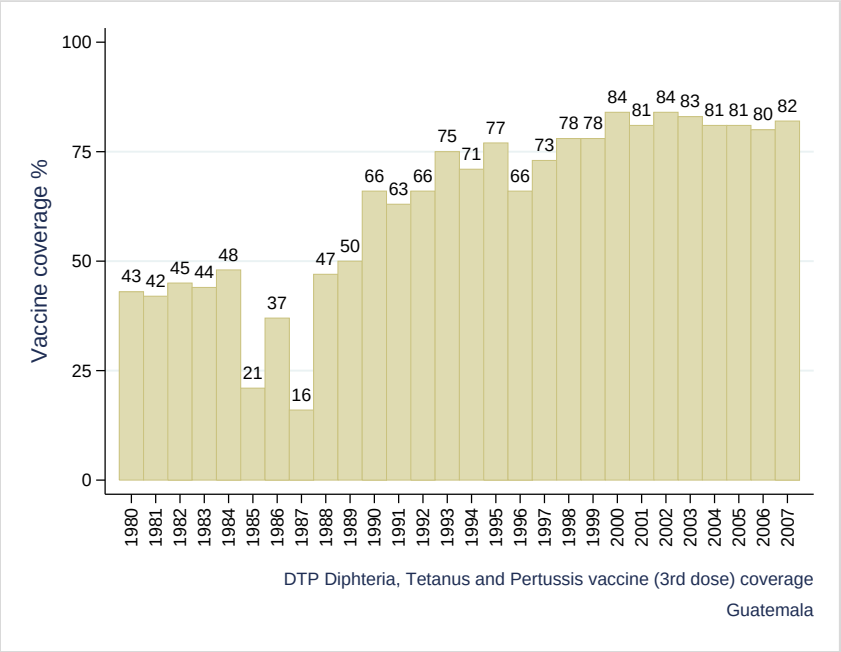
Table 40: General immunization schedule in Guatemala

Vaccine	Schedule	Coverage†	Comment
Bacille Calmette-Guérin vaccine	birth	entire	-
Diphtheria and tetanus toxoid with whole cell pertussis vaccine	18 months; 4 years	entire	-
Diphtheria and tetanus toxoid with whole cell pertussis, Hib and HepB vaccine	2, 4, 6 months	entire	-
Influenza	> 60 years	entire	and HCWs
Measles mumps and rubella vaccine	12 months	entire	-
Measles and rubella vaccine	9-39 years	entire	special groups
Oral polio vaccine	2, 4, 6, 18 months; 4 years	entire	-
Tetanus and diphtheria toxoid for older children / adults	1st contact; +1, +6 months; +1, +1 year	entire	Women from 15 to 49 years
Vitamin A supplementation	6,12,18,24,30,36 month	entire	-

†Entire or part of the population covered.
Notes and sources:
WHO Immunization surveillance, assessment and monitoring (http://www.who.int/immunization_monitoring/data/data_subject/en/)

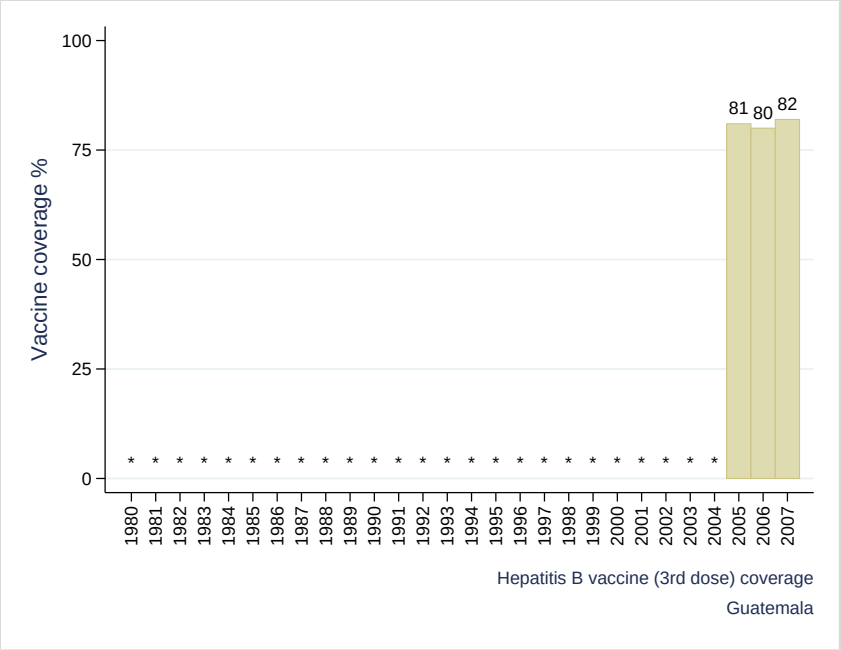
8.2 Immunization coverage estimates

Figure 32: DTP (Diphtheria, Tetanus and Pertussis) vaccine coverage (3rd dose completed) in Guatemala



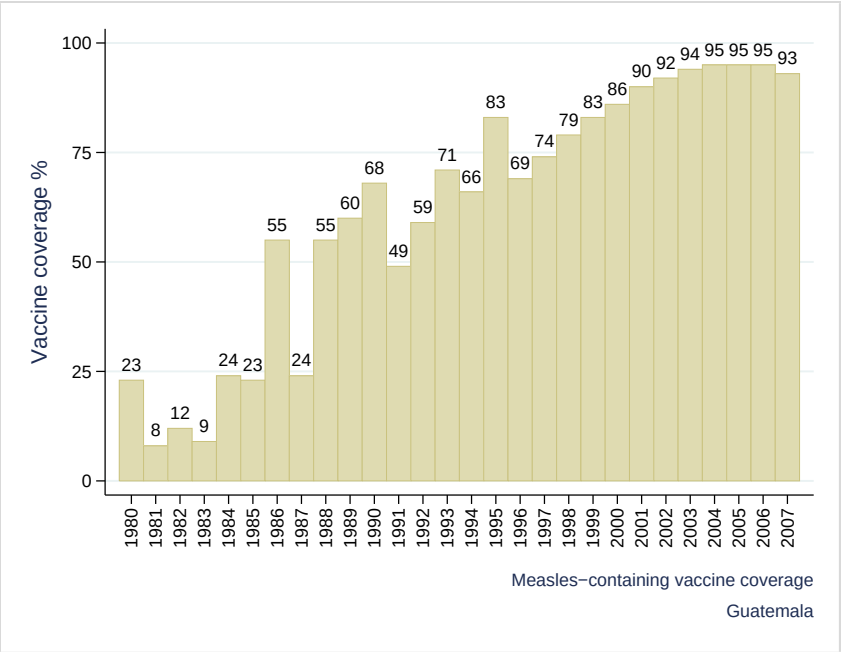
∗Data not available
Data sources:
WHO Immunization surveillance, assessment and monitoring (http://www.who.int/immunization_monitoring/data/data_subject/en/)

Figure 33: Hepatitis B vaccine coverage (3rd dose completed) in Guatemala



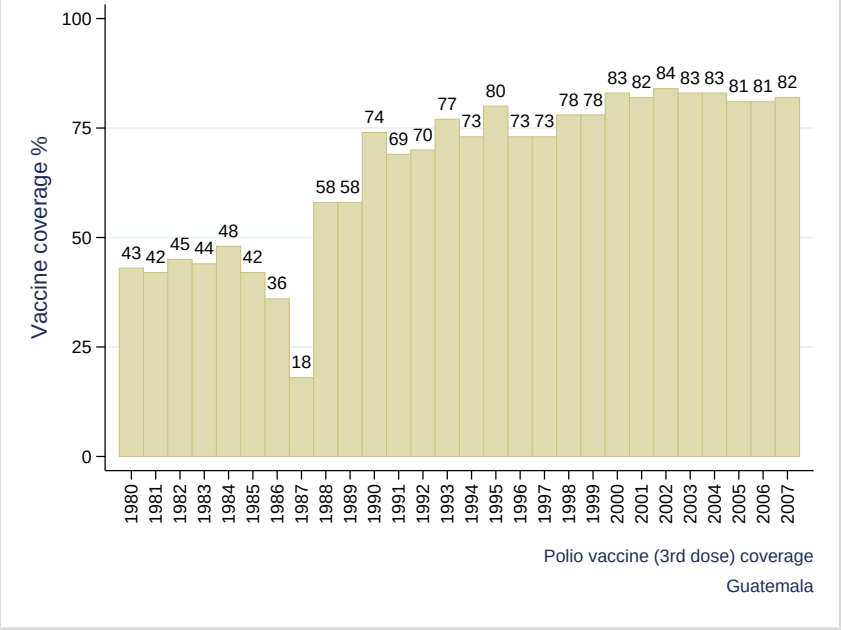
∗Data not available
Data sources:
WHO Immunization surveillance, assessment and monitoring (http://www.who.int/immunization_monitoring/data/data_subject/en/)

Figure 34: Measles-containing vaccine coverage in Guatemala



∗Data not available
Data sources:
WHO Immunization surveillance, assessment and monitoring (http://www.who.int/immunization_monitoring/data/data_subject/en/)

Figure 35: Polio vaccine coverage (3rd dose completed) in Guatemala



∗Data not available
Data sources:
WHO Immunization surveillance, assessment and monitoring (http://www.who.int/immunization_monitoring/data/data_subject/en/)

8.3 Other immunization indicators

Table 41: Relevant indicators of vaccine implementation in Guatemala.

Indicator		Value[a]
Immunization planning and management	Does the country have a multi-year plan (MYP) for immunization?	No
	What years does the MYP cover?	-
	Is MYP costing included?	-
	Is the MYP for immunization integrated into the broader health sector plan?	-
	Year of last inventory (models: location; age and working status) of all refrigeration equipment assigned for public immunization services in the country	2005
Immunization system performance	Total number of districts in country	332
	% of districts >=80% DTP3 coverage	92
	Drop-out rate between DTP1 and DTP3 coverage	3.32
Surveillance	Is there a system in place, with laboratory confirmation, to measure the impact of vaccination against invasive bacterial diseases, for example bacterial meningitis or pneumonia?	Yes
Safety	Non AD disposables: Type of injection equipment used for routine immunizations	No
	Sterilizable: Type of injection equipment used for routine immunizations	No
	Are safety boxes distributed with all vaccine deliveries?	Yes
	Was there any monitoring for immunization safety (i.e. monitoring of adverse events following immunization)?	Yes
Finance	Was there any monitoring for immunization safety (i.e. monitoring of adverse events following immunization)?	Yes
	What percentage of routine vaccine costs was financed by the government (including loans)?	-
	Was there a line item in the national budget for purchase of injection supplies (syringes: needles, sharp boxes) for routine immunizations?	Yes
	% of immunization spending financed using Government funds	-
New vaccine introduction	Is Hepatitis B vaccine integrated into the routine immunization systems?	Yes
	Is Rubella vaccine integrated into the routine immunization systems?	Yes

'A' means Adolescents, 'E' means Estimates and 'P' means Partial.
Reported for year: [a] 2007;
Data sources:
WHO Immunization surveillance, assessment and monitoring (http://www.who.int/immunization_monitoring/data/data_subject/en/)

Note to the reader

Anyone who is aware of relevant published data that may not have been included in the WHO/ICO Information Centre on HPV and Cervical Cancer is encouraged to contact the HPV Information Centre for potential contributions.

Although efforts have been made by the HPV Information Centre to prepare and include as accurately as possible the data presented, mistakes may occur. Readers are requested to communicate any errors to the HPV Information Centre, so that corrections can be made in future volumes.

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A systematic review of national immunization policy making processes☆

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ABSTRACT

This systematic review aimed to collect and synthesize information available on immunization policy making processes in countries across the globe. Twenty-nine published articles and five websites in either English or French provided varied information on the immunization policy making processes in 33 countries. The information retrieved varied from players involved to types of evidence used when making immunization policies. Fourteen countries reported the presence of a National Immunization Technical Advisory Group (NITAG), an advisory body that provides immunization recommendations to the national government to facilitate their policy making. In conclusion, there is relatively limited information available on immunization policy making processes at the national level.

1. Introduction

Although virtually all countries have a National Immunization Program of some kind, the processes leading to decisions on which vaccines to include are not well described. Yet it is important to understand how vaccine policies are developed given the amount of money spent on vaccines, the increased prices of newer vaccines, the fact that vaccines guard against some of the most deadly diseases, and that they are among the most effective of public health interventions. To facilitate the immunization policy making process, some countries have established national technical advisory bodies, often referred to as National Immunization Technical Advisory Groups (NITAGs). These are ideally independent, expert advisory committees that provide technical advice on vaccines and immunizations and make recommendations to guide policy makers and program managers [1]. As information on the presence, characteristics and functioning of these groups appeared limited, we conducted a systematic review of all information available on immunization policy making processes at the national level, including the presence and characteristics of NITAGs.

2. Methods

2.1. Eligibility criteria

Publications, reports and government websites were eligible for inclusion in this review if they contained a description of the process of immunization policy making at a national level. Countries were defined as member states of the World Health Organization (WHO) for the purpose of this article [2]. Because the primary author (MB) has working knowledge of English and French, publications, reports and websites in these languages were eligible for inclusion. Additional eligibility criteria included:

1. Description of immunization policy making processes including players and/or factors involved.
2. The processes described must be that of the national level of a specified country.

2.2. Search strategy

The search strategy was developed in the database Medline using the OVID platform and adapted to another database, Global Health. The search strategies combined a search for immunization or vaccination as well as a search for policy making or decision making in Medline (1950–April Week 2, 2008) and Global Health (formerly CAB Health) (1973–April 19, 2008) (Fig. 1). The search strategies were not restricted by language or date.

The secondary references of eligible studies were screened to determine if any of the references could potentially be included in the review.

Abbreviations: NITAG, National Immunization Technical Advisory Groups; UK, United Kingdom; USA, United States of America; WHO, World Health Organization.

☆ One of the authors is a staff member of the World Health Organization. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy or views of the World Health Organization.

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OVID Medline

#1 ((((immuni* or vaccin* or innoculat*) in ti,ab) or ((explode "Immunization-" / all SUBHEADINGS in MIME,MJME,PT) or (explode "Vaccines-" / all SUBHEADINGS in MIME,MJME,PT) or (explode "Immunization-Programs" / all SUBHEADINGS in MIME,MJME,PT)))

#2 ((((mak* or responsib* or authori*) near3 (policy or policies or decision*)) in ti,ab) or ((explode "Decision-Making" / all SUBHEADINGS in MIME,MJME,PT) or ("Policy-Making" / WITHOUT SUBHEADINGS in MIME,MJME,PT))))

#1 and #2

Global Health

1) TI mak* N3 polic* or TI responsib* N3 polic* or AB mak* N3 polic* or AB responsib* N3 polic*

2) TI mak* N3 decision or TI responsib* N3 decision or AB mak* N3 decision or AB responsib* N3 decision

3) TI immuni* or AB immuni* or TI vaccin* or AB vaccin* or TI innoculat* and AB innoculat*

4) TI authori* N3 polic* or TI authori* N3 decision or AB authori* N3 decision or AB authori* N3 polic*

5) decision making or policy making

6) 1 or 2 or 4 or 5

7) 6 & 3

Fig. 1. Search strategies.

The search for grey literature was limited to the search of government websites and contact with experts. Experts who had recently worked in the topic area with the WHO headquarters were asked if they knew of any publications or reports on the topic that were not retrieved through the literature search.

The government websites of the 193 member states of the WHO were searched for information on the immunization policy development processes of the countries. When possible, government websites were accessed using a list of national government websites created by the University of Michigan [3]. When the country was not listed on this website, government websites were searched for using the Google search engine with the key words of "government" and "official" and the name of the country [4]. Once the government official website was accessed, the information on immunization policy development processes was sought by navigating through Ministry of Health or Public Health websites and other relevant pages such as that of immunizations and vaccines. The search of websites was also restricted to those in English or French.

2.3. Selection of publications

All titles and abstracts (when available) of the citations identified were screened by two reviewers independently. All records that were identified as potentially relevant were obtained in full text. If there was disagreement between the reviewers as to which citations qualified for inclusion, the citation was included and the full text was obtained. The full text articles were screened by the two reviewers independently in accordance with the inclusion criteria.

2.4. Quality assessment

Because this systematic review was descriptive in nature and did not include clinical trials or qualitative research, the quality assessment of reports did not include the traditional components used to assess the quality of intervention or qualitative studies. The author's affiliation and the sponsorship of the article was used as an indication of potential conflict of interest, as well as the date of publication as an indication of the extent that the information may be dated.

3. Results

3.1. Selection of published information

The literature search yielded 1530 potential publications for inclusion in this review. Ovid Medline yielded 1213 of the citations and Global Health another 317. Of the citations, 128 papers (94 from Medline and 34 from Global Health) were retrieved as potential candidates for inclusion based on their titles and abstracts. After review of the full papers, only 26 publications contained descriptions of immunization policy making processes at a national level. Eight of the publications were retrieved from both Medline and Global Health [5–12], while another 14 publications were retrieved from Medline only [13–26], and another four from Global Health only [27–30].

Beyond the 26 publications obtained through the literature search, 3 additional publications were included: one from reference sections of the included papers [31], one was provided through contact with an expert in the area [32], and one from the Canadian website on their NITAG. It is unknown why these publications were not obtained through the search strategy.

The websites of five of the countries provided information on national immunization policy development: Australia [33], Canada [34], New Zealand [35], the United Kingdom (UK) [36], and the United States of America (USA) [37]. Therefore, this review is based on the content of 29 publications and 5 websites.

Table 1
Characteristics of policy processes and National Immunization Technical Advisory Group (NITAG) by country with information available on immunization policy development[a].

Country	NITAG	Core members	Defined term limit for members (years)	Declare conflicts of interest	Meetings per year	Nature of meetings	Meeting minutes published on the internet	Method of final decision making	Other group that makes immunization recommendations [b]
Australia	Yes				3	Closed	Yes		
Austria	Yes	16	3		3		No		
Belgium									Yes
Brazil	Yes								
Bulgaria									Yes
Cambodia									Yes
Canada	Yes	12	4	Yes	3	Closed	Yes	Vote	
Denmark									Yes
France	Yes	16			6–8	Closed	No		
Germany	Yes	17			2				
Greece									Yes
Ireland	Yes		No		6	Closed	No	Consensus	
Italy	Yes								
New Zealand	Yes								
Luxembourg									Yes
Norway									Yes
Papua New Guinea									Yes
Portugal									Yes
Spain	Yes		No					Consensus	
Slovakia									Yes
Slovenia									Yes
Sweden									Yes
Switzerland	Yes	15	4		5	Closed	No	Vote	
Thailand									Yes
The Netherlands	Yes								
UK	Yes	16	4	Yes	3	Closed	Yes	Vote	
USA	Yes	15	4	Yes	3	Open	Yes	Vote	

[a] Blank fields indicate that information was not available—also limited information was available on Argentina, China, Finland, Iceland, Mali, and Poland but not related to the information in this table.
[b] Unknown if these groups are NITAGs as defined in this paper.

3.2. Characteristics of included publications

The 29 publications and 5 websites from which information was abstracted contained information to varying degrees on immunization policy decision making processes in 33 of the 193 WHO member states: Argentina [19], Australia [10,13,23,33], Austria [20,32], Belgium [20], Brazil [5], Bulgaria [20], Cambodia [8], Canada [10,14,31,34,38], China [27], Denmark [15,20], Finland [20], France [17,20,32], Germany [20,32], Greece [20], Iceland [20], Ireland [17,32], Italy [20,32], Luxembourg [20], Mali [9], New Zealand [6,30,35], Norway [12,20], Papua New Guinea [28], Poland [20], Portugal [10,20], Slovakia [20], Slovenia [20], Spain [17,20,32], Sweden [17,20,32], Switzerland [10,17,32], Thailand [7], The Netherlands [10,11,14,20,32], the UK [17,20,24,26,32,36], and the USA [16,18,21,22,25,26,29,37]. The most detailed information was found in publications concerning immunization policy making processes in the UK [24] and the USA [25] as well as on the websites of Australia [33], Canada [34], the UK [36], and the USA [37].

Two publications focused primarily on the process of immunization policy making within a country (the UK and the USA) and discussed a NITAG in detail [24,25]. Fourteen of the publications mentioned NITAGs in the context of discussing a specific issue such as a specific vaccine but did not offer much information on the NITAG [5,6,10,13,14,18,19,21–23,26,29–31]. The five websites provided extensive information on the NITAGs in Australia [33], Canada [34], New Zealand [35], the UK [36], and the USA [37].

3.3. Quality assessment

All authors stated affiliations which were consistent with vaccine policy stakeholders. These included members of the Ministry of Health or local universities and often both. Only two of the publications in this review were sponsored by pharmaceutical companies [6,12]. A publication from New Zealand was a collaboration between the national government, Chiron Vaccines, and the University of Auckland but provided only the fact that a NITAG exists [6]. A study from Norway was sponsored by Wyeth Lederle [12], but focused on a cost effectiveness analysis of the 7-valent pneumococcal conjugate vaccine. It is unlikely that the sponsorship of either of these papers affected the quality of the publication with respect to this review.

3.4. National policy development processes

Information was retrieved on the immunization decision making processes in 33 countries (Table 1). Belgium [20], Bulgaria [20], Cambodia [8], Denmark [15,20], Greece [20], Luxembourg [20], Norway [20], Papua New Guinea [28], Portugal [10], Slovakia [20], Slovenia [20], and Sweden [17,32] reported groups which make immunization recommendations to the government. However it was unclear from the information collected if these groups were NITAGs that are independent from the national government as defined by the WHO [1]. Cambodia has a national level immunization technical working group that identifies, implements, and monitors National Immunization Programs in Cambodia [8]. However, the members listed are government officials and representatives of international donors. In Papua New Guinea, the National Pediatric Society makes recommendations and publishes guidelines that serve as standards of care by the Health Department [28]. Denmark has a National Board of Health [15,20], Portugal has the National Vaccination Plan committee [10] and Sweden has a governmental advisory agency [15,32] that make national immunization recommendations. The National Board of Health in Denmark conducts a medical technology assessment [15] and mathematical modeling [20] when making immunization policy decisions. This board considers various types of evidence (Table 2).

Table 2
Factors considered by countries when making recommendations by presence of National Immunization Technical Advisory Groups reported[a].

Factors considered when making recommendations	Countries with NITAG	Other countries
Burden of disease	Canada [31,34] Netherlands [14,32] Spain [32] USA [37]	Argentina [19] China [27] Denmark [20] Finland [20] Iceland [20] Mali [9] Portugal [20] Poland [20] Sweden [20,32]
Economic evaluation	Canada [10,34] Netherlands [10,11,32] Switzerland [32] UK [24,36] USA [37]	Argentina [19] China [27] Denmark [20] Finland [20] Iceland [20] Luxembourg [20] Norway [12] Portugal [20] Sweden [20]
Feasibility of local vaccine production		China [27]
Feasibility of recommendation	Canada [31]	Argentina [19]
Recommendations of other countries	Brazil [5] Canada [34] Switzerland [32] UK [37]	
Public perception		Argentina [19] Denmark [20]
Vaccine safety	Canada [14] Spain [32] USA [37]	Argentina [19]
Vaccine effectiveness	Canada [14] Spain [32] USA [37]	Argentina [19]

[a] Additional factors may be considered in process. This table presents factors specifically reported.

The advisory committee in Norway also uses mathematical modeling when making immunization policy decisions [20]. In the USA, although they have the Advisory Committee on Immunization Practices (which is an independent NITAG), they also have the American Academy of Pediatrics [22,29], the American Academy of Family Physicians [20,22], the American College of Gynecologists and Obstetricians [25], and the American College of Physicians [25] all of whom make immunization recommendations. Efforts are made to harmonize recommendations between these groups [25].

The information retrieved on Thailand concerned the development of the national hepatitis B immunization policy in which many players were involved [7]: the Ministry of Public Health's Department of Communicable Disease Control, the Thai Medical Association, the pharmaceutical industry, and the media. A committee was formed with representations of government, as well as various institutes and associations. It could not be determined from the publication whether this committee and these groups are involved in making all immunization policy decisions, or were only involved for this one vaccine.

The information obtained on the remaining eight countries relates to the types of evidence used when making decisions (Table 2). Burden of disease and economic assessment are the most commonly reported types of evidence used by countries when making immunization policies.

3.5. National Immunization Technical Advisory Groups

While many countries may have established NITAGs, their presence was reported in only 14 countries (Australia [10,13,23,33], Austria [17,20,32], Brazil [5], Canada [10,31,34,38], France [17,20,32], Germany [17,20,32], Ireland [17,32], Italy [17,32], New Zealand [6,30,35], Spain [17,20,32], Switzerland [17,32], The Netherlands [10], the UK [17,20,24,26], and the USA [16,18,21,22,25,26,29,37]). There were no reports of NITAGs which had been in existence but were no longer functioning.

Generally, the NITAGs in each country provided advice and guidance to the government on the administration of vaccines to the population. For example, the terms of reference for the Australian NITAG are to provide technical advice on the administration of vaccines available in Australia, advise on and assess the evidence available on existing, new and emerging vaccines, produce the Australian Immunization Handbook, and consult with partners on matters relating to the implementation of the Australian Immunization Program [33].

It is unknown when most of the NITAGs were established, as the dates of the creation of the NITAGs were only provided for 5 of the 14 countries. The NITAG in the UK was established in 1963 [24,36], Canada [34] and the USA [25] in 1964, France in 1997 [32], and Switzerland in 2004 [32]. Although the exact year is not reported, the NITAG in New Zealand has existed since at least 1980 [30].

Of the 14 countries for which information on their NITAGs was retrieved, 12 countries provided information on their membership (all except Brazil and New Zealand) [13,16,17,24,25,32,34,36,37]. The number of members was reported for 8 of the NITAGs and varied from 12 to 17 (Austria, Canada, France, Germany, Ireland, Switzerland, the UK, the USA) [16,17,24,25,32,34,36,37]. Five of the countries reported that a defined term is given for members which lasts three to four years (Austria, Canada, Switzerland, the UK, the USA) [17,25,32,34,36,37] while the reports for Italy and Spain indicated that there is no defined term limit for committee members [32]. The chair of the committee is referred to for three of the NITAGS: Canada, France, and the USA [22,32,37]. There were between 4 and 15 ex-officio members reported by 5 of the committees [16,24,25,32–34,36,37] and between 11 and 27 liaison members reported by two committees [16,25,34,37].

All members on the NITAGs in Canada, the UK, and the USA must declare potential conflicts of interest [25,34,36,37]. In the case of a conflict of interest, the member may be excluded from the final decision making [34,36,37] or if the conflict is significant, they may have to resign [25].

The types of expertise represented on the NITAG was reported for Canada, France, Germany, Italy, New Zealand, Spain, Switzerland, the UK, and the USA [13,16,24,25,32,34–37]. These included clinical medicine, epidemiology, immunology, health economics, health planning, infectious disease, internal medicine, microbiology, nursing, pediatrics, public health, and vaccine research while some also had a community member or an insurance representative. The most commonly reported areas of expertise were infectious disease ($n=5$) followed by immunology, microbiology, pediatrics, and public health, which were all represented on four of the nine committees.

Nine of the 14 NITAGs had a defined number of meetings, of which the majority ($n=5$) met three times per year [24,25,32–34,37]. The highest number of meetings per year was reportedly held by the NITAG in France which met six to eight times per year [32], while the NITAG in Germany met only twice a year [32]. Six of the NITAGs held closed, confidential meetings (Austria, Canada, France, Ireland, Switzerland, the UK) [24,32,34], while only the NITAG in the USA had meetings open to the public [25,27]. Of the eight countries which reported taking meeting minutes, half of the countries published them on the internet (Australia, Canada, the UK, the USA) [24,25,33,34,36,37] and the other half did not publish them (Austria, France, Ireland, Switzerland) [32].

Information was given on the use of evidence in 8 of the 14 NITAGs (Table 2). Australia mentioned using evidence but did not offer further information [10,13,33]. The NITAGs in Brazil [5], Canada [34,38], and the UK [36] conduct a literature review prior to making recommendations. It was reported that the NITAG in Canada [34,38], the UK [36], and the USA [25] appraise the quality and validity of the evidence to determine if it is strong enough to justify a recommendation in their countries. Canada [34,38] and the USA [25] reported grading the evidence, while the UK's method was not specifically reported [36].

Details about the publication of NITAG recommendations are given for nine countries. While Australia [33], Austria [32], Germany [32], and the UK [24,36] produce an annual report or annual national immunization booklets including the recommendations of the NITAG that were accepted by the government, France and Ireland [32] publish their guidelines every second year in a report. Austria, Canada, New Zealand, the UK, and the USA publish their recommendations online [24,25,32,34–37].

4. Discussion

This systematic review is the first known attempt to retrieve and summarize information published about the processes of immunization policy making at a national level. Although every country with an Immunization Program presumably has gone through the process of developing their national immunization policies, the information published and available online about the process of immunization policy development was relatively limited being obtained from only 33 of 193 countries. Further, the amount of information available varied tremendously by country with the most information available on the processes in Australia, Canada, the UK, and the USA for which the information described was fairly comprehensive.

The main limitation of this review is that only publications, reports and websites in English or French were included in the review. There is likely to be additional information available on the processes of immunization policy making at a national level published in languages other than English or French, particularly on national websites, though we were unable to determine to what extent.

The assessment of the quality of information is another limitation of this study. Although the source and date of publication were documented, national policy making processes may have changed over time and it is unknown if the methods employed in the past remain the same today. As well, there are many varying perspectives of players involved in immunization policy development that may not have been reflected in the published literature due to the small number of publications and limited information provided.

Granted the above-mentioned limitations, the lack of detailed information retrieved in print and on the web points to a need for countries to enhance dissemination of information on their immunization policy making processes. This exchange of information could help countries improve their policy making processes by offering concrete examples of feasible policy making methods. Also, governments publishing their decision making processes would increase the credibility and transparency of immunization policy development.

The information retrieved about the immunization policy making processes came mostly from industrialized countries [39], however, there was information about four countries considered to be developing (Brazil, China, Papua New Guinea, and Thailand) and two countries considered to be least developed (Cambodia and

Mali). For the developing and least developed countries, the information retrieved briefly described the players involved and factors considered when making immunization policies. Overall, there was little information available about the processes of immunization policy development particularly in developing countries.

The 14 countries with NITAGs for which information was retrieved in this review are all developed with the exception of Brazil. Brazil is considered a developing country by the United Nations [39], but is known for its strong public health system. Although there are presumably many NITAGs in existence, only 14 were identified in print literature and country websites and limited information about them was published. There is little published or easily accessible website information on the NITAGs outside of those in Australia, Canada, the UK, and the USA, at least in the English and French languages. This reinforces the need for countries to publish information on their immunization policy development processes such as the presence and functioning of NITAGs.

The information collected in this review revealed many differences between countries' NITAGs. Although they have the same purpose, the methods of functioning, membership, decision making processes, and the transparency of the processes vary among groups. The reported modes of functioning of each NITAG are consistent with their purpose but vary according to the context each country.

Of note is that there were no reports of a country that had an NITAG and subsequently dissolved it. Countries wishing to form a NITAG should consider their specific needs and resources and may want to use models developed in other countries to ensure credibility, transparency, accountability, stability, and independence.

No data on process or outcome evaluation of immunization policy making were available in the literature reviewed. This is an important gap in the literature and such an assessment may need to be done in order to convince some governments of the credibility and usefulness of these groups.

This review is a concise presentation of the information retrieved from public sources on immunization policy development processes around the world. Given the effect of vaccines on population health and the vast sums of money needed and spent on vaccines, more attention on the immunization policy development processes is needed in order to document best practices which may benefit all countries. In itself, the scarcity of information raises the question of policy effectiveness and reinforces the need for increased publication to remedy the information gap on immunization policy making processes across the globe.

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Conflict of interest statement

The authors state that they have no conflict of interest.

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