Cervical Cancer Burden and Prevention Strategies: Asia Oceania Perspective

Suzanne M. Garland1,2,3,4, Neerja Bhatla5, and Hextan Y.S. Ngan6

Abstract

The Asia Oceania region contributes to more than 50% of cervical cancer cases worldwide. Yet cervical cancer is one of few cancers that can be prevented through comprehensive screening for precancerous lesions, with their subsequent treatment. Screening with cervical cytology, a very old technology, has reduced cervical cancer mortality and incidence when applied in comprehensive programs with high coverage and high quality assurance. However, of those countries within this region that have set up such programs, many have been opportunistic, had poor coverage, or inadequate treatment facilities for lesions found. Consequently, they have not seen large reductions in cancer incidence or mortality. Some have therefore adopted visual inspection by acetic acid (VIA) and Lugol’s iodine (VILI) or human papillomavirus (HPV) DNA assays for screening.

With two safe, immunogenic and efficacious prophylactic vaccines licensed, the way forward to reduction of cervical cancer to becoming uncommon is within reach. Where governments have supported high coverage public-health vaccination programs, reductions in disease burden with shortest incubation (genital warts, high-grade abnormalities) are already being reported. One of the biggest impediments is the cost of vaccines that are affordable to resource-poor countries. Other challenges include, infrastructure for delivery of vaccines, plus general acceptance of vaccination by the community.

Current Cervical Cancer Burden: Incidence and Mortality

The incidence of cervical cancer varies widely around the world, with the highest burden of disease occurring in less developed regions, largely reflecting lack of screening programs. The Asia Oceania region accounts for just more than 50% of all cases and deaths from the disease worldwide, with (1) South Central and Southeast Asia having the highest incidence and mortality rates.

Every year across the Asia Oceania region almost 315,000 women are diagnosed with cervical cancer giving an overall incidence of 15.2 of 100,000: this is likely an underestimate (1). Some of the highest age-standardized rates (ASR) include Nepal (32 of 100,000), Mongolia (28.4 of 100,000), India (27 of 100,000), and Papua New Guinea (PNG; 23.2 of 100,000). The Asia Oceania Research Organisation in Genital Infections and Neoplasia (AOGIN) is a society set up to promote education and research to decrease the incidence of cervical cancer in the Asia Oceania region. (see Fig. 1 for some representative examples of AOGIN member country cervical cancer incidence rates).

There are similar patterns of mortality rates to incidence across the Asia Oceania region, with around 160,000 women dying from cervical cancer annually: an overall ASR of 7.9 of 100,000. Examples of highest rates reported are Nepal (17.6 of 100,000), PNG (17.6 of 100,000), India (15.2 of 100,000), and for mid-resource countries such as Thailand, 12.8 of 100,000. This is in contrast to low mortality rates in Japan (2.6 of 100,000) and Australia (1.8 of 100,000; see Fig. 2 for cervical cancer mortality rate for the Asia Oceania region) (1). For individual country details of cancer incidence, mortality, trends, and prevention strategies, the reader is referred to the monograph for the Asia Oceania region in a special supplement of Vaccine 2008 (2–9).

While cervical cancer is the second most common cancer among women within Asia Oceania, mortality rates are lower than other cancers (lung, stomach, and breast; see Fig. 3).

Cervical Cancer Screening

Differences in incidence and mortality rates for cervical cancer across Asia Oceania largely relate to the existence or not of well-organized, well-controlled, high-quality...
cervical cytology screening programs with good coverage of the appropriate target population. This is largely contingent on a wide variability in economy in populations within, as well as between countries, a great diversity in culture (ethnicities, traditions, religions, and nationalities), and in some countries a wide variation in recognition of women’s rights.

For example in Australia, a high resource country, between the commencement of a well-organized Pap program in 1991 and 2005, the incidence of cervical cancer in women of all ages decreased from 12.7 to 6.9 of 100,000 (age standardized to the Australian population) while the mortality rate decreased from 4.0 of 100,000 in 1991 to 1.8 of 100,000 women in 2007. Despite Australia’s comprehensive Pap screening program (2 yearly from 18 years of age or 2 years after first sexual intercourse) only about 60% of eligible women have tests 2 yearly. Moreover, most women diagnosed with cervical cancer have not had regular Pap.

In less resource-rich countries, cervical cytology screening varies from nil [e.g., Mongolia (9), opportunistic screening only, e.g., India, Nepal, China, Bangladesh, Sri Lanka (6), to more comprehensive but only relatively recently commenced screening programs, Singapore, Hong Kong (3)]. For other countries, alternative screening programs such as visual inspection with acetic acid (VIA)
and Lugol’s iodine (VILI) are being used (e.g., India, Bangladesh, Philippines, Thailand) (6). The rapid affordable human papillomavirus (HPV) DNA test (CareHPV, Qiagen Inc.) has undergone trials in China with great success: once this is available commercially it has the potential to be a more effective option for wide use in those countries with no organized screening programs (12).

Details for various countries screening policies, including the type of screening used, are detailed in the special monograph supplement of Vaccine (2–9). Table 1 also illustrates some examples of various cervical cancer screening programs in representative AOGIN countries.

Relative contribution to cervical cancer by oncogenic HPV genotypes

The relative contribution of the 8 most common types in cervical cancer worldwide are reported consistently for HPV 16+18 (70.8%); 16+18+45 (76.7%); 16+18+45+33+31 (84.2%); whereas the proportional attribution of 16+18+45+33+31+52+58+35 is 91.3% (13). This pattern is generally similar for the Asian Oceania region being, respectively, 71.6%, 77.2%, 83.7%, and 92.4% (13). For India HPV 16 and 18 account for 82.5% (14). Some countries (Taiwan, Hong Kong, and Singapore who are primarily constituted of Han Chinese, who share common ancestors from the south-eastern coast of China) report a pattern of relative preponderance of HPV 52 and 58, after HPV 16 and 18 (15–19).

Primary prevention opportunities

Following the success of phase III clinical vaccine trials of bivalent and quadrivalent HPV vaccines and which have subsequently been licensed for use at a public health level, we now have the tools for reducing the bulk of cervical cancers. This goal is however dependent on appropriate high coverage in the target population of young girls and/or young boys before they become sexually active (20). The potential effects are well shown from the early reports from the government-funded school-based vaccine commenced early 2007 in Australia. This program targeted girls of ages 12 to 18 years in schools, with a catch up program of young women to 26 years and largely delivered through general practices, commencing in July 2007 and finishing December 2009. The program is ongoing for 12-year-old girls and to date has just more than 70% coverage for 3 doses coverage (21).

Recently reported is a significant decline in the frequency of genital warts in young Australian women as well as heterosexual men in the same age group, but not among women older than 26 years in July 2007, nor for men who have sex with men (22). These data suggest that vaccination could be responsible for a reduction in clinical symptoms and signs due to HPV 6/11 infection, with protective effects in heterosexual men through herd immunity, as early as 2 years postvaccination, and hence an expected reduction in vaccine-related HPV carriage, with a reduction in CIN3 henceforth, given that Australia is now in its sixth years cohort of vaccination of school girls. Also reported from Victoria Australia is detected a decrease in incidence of histopathologically confirmed high-grade cervical abnormalities, in females <18 years within 3 years of the implementation of the HPV vaccination program (23).

Very recently reported from Australia, and after four years from commencement of their vaccine program, is a substantial fall in vaccine targeted genotypes, with lower prevalence observed in both vaccinated as well as unvaccinated women compared with prevaccination populations (24).

While many countries within the Asian region have licensed bivalent and/or quadrivalent vaccines, in general the target has been in private markets and only for those who can afford the vaccine (see Table 1 for examples...
<table>
<thead>
<tr>
<th>Vaccines licensed (year of licensure)</th>
<th>Resources</th>
<th>Recommendations</th>
<th>Coverage to date</th>
<th>Cervical cytology/via/HPV DNA</th>
<th>Opportunistic/organized</th>
<th>Target population screening intervals and estimated coverage</th>
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<tbody>
<tr>
<td><strong>Australia</strong></td>
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<td></td>
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<td></td>
<td>Catch up to 26 years from July 2007 to December 2009</td>
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<td></td>
<td>Two yearly currently under review (renew program)</td>
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<td>2012 agreement to vaccinate all boys between 12–13 y (yet to be commenced and funded by the government)</td>
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<td>60% coverage</td>
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<td><strong>New Zealand</strong></td>
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<td></td>
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<td>Catch up age 13–18 y</td>
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<td><strong>India</strong></td>
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<tr>
<td>Bivalent (2008) and quadrivalent (2008)</td>
<td>In private market only</td>
<td>Approved by (i) Indian Academy of Paediatrics (IAP); (ii) Federation of Obstetrics &amp; Gynaecology Societies of India (FOGSI); and (iii) Association of Physicians of India (API). Recommend for administration between 10–14 y (i), ideally 10–14 y or before sexual debut, but licensed for use till age 45 years (ii) and (iii).</td>
<td>No data available</td>
<td>Cervical cytology, VIA, HPV DNA</td>
<td>Opportunistic</td>
<td>70–75% coverage</td>
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<td>VIA 1.5 million/annum</td>
<td>2.6% (women aged 18–69 y were screened every 3 y)</td>
<td>20,000 HPV DNA/annum</td>
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<table>
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<tr>
<th>Vaccines licensed (year of licensure)</th>
<th>Resources</th>
<th>Recommendations</th>
<th>Coverage to date</th>
<th>Cervical screening via HPV/DNA</th>
<th>Target population</th>
<th>Screening intervals and estimated coverage</th>
<th>HPV vaccinations</th>
</tr>
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<tr>
<td>Thailand</td>
<td>Quadrivalent (2007)</td>
<td>None</td>
<td>No data available</td>
<td>Cervical cytology, VIA in some areas</td>
<td>Cervical cytology</td>
<td>Both organized and opportunistic</td>
<td>Bivalent (2007)</td>
</tr>
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(Continued on the following page)
of HPV vaccination status in some countries within the Asia Oceania region). Thus the impact of opportunistic vaccination will translate to little reduction in vaccine-related disease. Public health programs resulting in high coverage and supported by governments can only be a reality if costs can be reduced markedly. Moreover, development of strategies for widespread HPV vaccination implementation is multifaceted and requires significant commitments by government, multilateral agencies, scientific community, and regional societies such as AOGIN, global health partnerships between public and private sector organizations such as the GAVI Alliance (GAVI). GAVI is a public–private partnership of key stakeholders in global immunization and raises funds for vaccines with the focus on saving lives and protecting peoples health in the poorest countries. Partners include World Health Organization (WHO), UNICEF, the World Bank, research and technical agencies, nongovernmental organizations (NGO), Gates Foundations, industry, plus developing and industrial country governments (20, 25). GAVI is funded by the International Finance Facility for Immunisation (IFFIm) and the Advance Market Commitment (AMC). In addition, vaccine manufacturers contribute by offering nonprofit prices for the vaccines. The GAVI Board and its Procurement Reference Group have approved accepting the HPV vaccine pending its ability to raise the necessary funds to purchase it (26).

The recent news that GAVI is now endorsing and prioritizing HPV vaccines, and that the price from Merck for GAVI-eligible countries will be in the order of 5 U.S. dollars per dose, could now make this a reality. However, with the recent change of around 20 previously GAVI-eligible countries becoming ineligible will put extra financial burdens on these countries rolling out a public health program.

Some examples of how various programs supported by pharmaceutical manufacturers together with NGOs are assisting some resource poor countries in rolling out program follow henceforth. Vaccine delivery strategies include school-based, community health center-based or outreach programs.

An example is Bhutan. As part of a 6-year program, Merck will provide the Gardasil (6, 11, 16, and 18) free in the first year to girls and young women in Bhutan, and at a concessional price for the remaining 5 years. Merck will also provide additional support for implementation of the program. The Australian Cervical Cancer Foundation (ACCF), a charity whose mission is to minimize the incidence and burden of cervical cancer is supporting the national vaccination program by providing financial support to the Government of Bhutan to secure doses of Gardasil at the access price after the first year. The Royal Government of Bhutan is committed to ensuring sustainability of this program beyond the 6-year partnership with Merck and ACCF. The pilot phase began from October 2009 to April 2010 with targeting of girls 11 to 13 years as a school-based initiative. It is noteworthy that 94% completed 3 doses. With the
national scale up (May–November 2010) 3 doses were completed in 97% of 12-year olds. Bhutan, therefore, will be the first low-income country in the world to implement a national cervical cancer vaccination program.

Other similar initiatives involving ACCF, also with very good take-up rates include programs in Nepal. A pilot program was initiated in 2009 and focused on secondary schools. Girls aged 10 to 26 years were offered vaccination (parental written consent was obtained) and 99% completed 3 doses. A national scale-up commenced in 2010 to 2011 (again 99% completed 3 doses) and is being extended.

A program in Fiji is Ministry led, with donations of vaccine from Merck. Of the target years of 9- to 12-year-old girls and as a school-based strategy, 62% obtained dose 1 and 39% 3 doses. Subsequently, a national mop up resulted in completion of dose 3 in 55%. A further national scale-up, which is planned for 2012, is being funded by an independent initiative by UNICEF.

PATH is an international nonprofit organization transforming global health through innovation, particularly focusing on culturally sensitive, high impact, low-cost solutions, and including distribution of vaccines.

In Vietnam a PATH led program has evaluated school-based delivery (38 schools) for girls in grade VI as compared with local health centers (72 local health centers for girls aged 11). Coverage was particularly high for 3 doses being 96.1% in schools and 98.6% for health centers (27).

India
In India, a PATH campaign approach achieved 77.2% to 87.8% coverage. Over two thirds of respondents gave as reasons for accepting the HPV vaccine as protection against cervical cancer, and refusal was more often driven by programmatic considerations (e.g., school absenteeism) than by opposition to the vaccine (27). The program came under a cloud in India amid allegations of ethical violations, but nevertheless provided important information about vaccine acceptability. It is noteworthy that India is no longer a GAVI-eligible country so cost is a concern.

Malaysia
The Malaysian government announced August 2010 that it would provide a national program for all 13-year-old girls. The bivalent vaccine was procured through tender and administered as a school-based program, as well as clinic based for those 13-year olds out of school and using existing health teams. It is noteworthy that Malaysia is the first middle-income country to introduce HPV immunization without outside financial support. It has been reported that parental consent forms returned with consent occurred at 95%. Also as of October 2011, acceptance of the third dose was 90.8%

Lessons learnt
From the comprehensive PATH programs, factors resulting in success included the following; secure visible government endorsement, training health workers teachers and others involved in the programs, well-coordinated planning and implementation, good communication and engagement of communities, appropriate education messages, having a crisis communication program in place.

Ultimately in resource poor countries, HPV vaccines may well be best placed within existing structures and resources of the expanded program on immunization (EPI). Within the various EPI such things as vaccine supply, transport, storage, monitoring, training, and other important parameters for a successful immunization program are already established.

Development of AOGIN
This relatively new Society of AOGIN was established to promote and develop, at an Asia-Oceania level, collaboration and research, scientific exchanges, education and training, development of information sharing, as well as conducting surveys and audits. Specifically for HPV-related diseases this has meant a focus on training and education in screening, detection, prevention, and treatment concerning genital infections, precancers, and cancers in women, and along the lines of EUROGIN which shared its expertise. AOGIN has a Board with a rotating Chair, formal Terms of Reference and a website (www.aogin.com (28)) The International Gynecologic Cancer Society (IGCS), Asia and Oceania Federation of Obstetrics and Gynaecology (AOFOG), and the International Papillomavirus Society (IPV) formally endorse AOGIN.

Each country within the region has different burdens of cervical cancer, economic status, political background, cultures, status of women’s rights, and resources available for cervical cancer control. Biennially, the members come together for a regional scientific conference, interspersed on the alternating year with an interim meeting. The Inaugural Conference of AOGIN was held on July 18 to 20, 2005, in Kota Kinabalu, Sabah, Malaysia, while the Philippines hosted the scientific meeting in Cebu the following year, followed by Seoul, South Korea for 2007, 2008, India hosted the interim meeting of 2009 in Kolkata, then New Delhi in 2010, with Bali, Indonesia in Hong Kong 2012. The conferences bring together clinicians (gynecologists, pathologists, infectious diseases physicians, sexual health physicians, gynecologic oncologists) and scientists whose work is related to genital infections and neoplasia.

Examples of research activities and communication initiatives:

i) Quantitative knowledge base
Collaborative research within AOGIN member countries has included quantitative work between Australia and Singapore in examining the knowledge base of HPV, cervical cancer screening, acceptability of prophylactic vaccines of Singaporean women (29)
and men (30). In general, in a computerized assisted telephone interview (CATI) approach, it was noted that there was a reasonable knowledge base on cervical cancer, but it was poor for HPV. There was however, general acceptability of the potential for vaccination, particularly when endorsed by the medical profession. Studies have been carried out on HPV epidemiology in the region: as well as meta-analyses (31, 32) of HPV distribution have been reported.

ii) Public education
To reach out to health workers, family doctors, pediatricians, governmental health agencies, and the general public at the 2008 conference AOGIN initiated an effort to broaden the scope of the conference and provide information and education to professionals involved with the lay public, working at governmental, and nongovernmental organizations and patient associations (8). Specifically, AOGIN endorses commitment to improve communication with patients, health authorities, professional organizations, and opinion leaders toward strengthening cervical cancer prevention in Asia, to achieve a timely steep reduction in this cancer (8). Each conference of AOGIN has since included public education as a major item on the program. The 2010 meeting liaised with the Women Against Cervical Cancer (WACC) group of EUROPE. AOGIN is to reach out to educators, media personnel, policy makers, and other members of civil society who influence attitudes to cervical cancer prevention in the community.

iii) Development of Asia Oceania Guidelines for the Implementation of Programs for Cervical Cancer Prevention and Control (33)
Recently AOGIN has developed guidelines for cervical cancer prevention with, for example, suggested algorithms of care for low-resource situations starting with VIA-based screening, or starting with affordable HPV testing. For high-resource situations, algorithms starting with parallel testing with cytology & HPV DNA testing, or commencing with HPV DNA testing, but then using reflex cytology and/or HPV genotyping (33).

Now that AOGIN has developed its own guidelines for the region, the next move is to draw less active member countries in the region to AOGIN. Our mission is to offer education and training on cervical cancer control, appropriate to the countries in our region. With collaborative efforts, we would like to conduct research addressing special situations in different countries with different background in the hope that the most cost-effective way in controlling cervical cancer can be recommended to the authority for implementation.

iv) Collaborations with Fiji
Cervical cancer in Fiji is at very high rates. The incidence and mortality rates is in the order of 49.7 per 100,000 and 32.3 per 100,000 for Melanesian Fijian women whereas the respective rates for those of Indo-Fijian women heritage are 35.2 per 100,000 and 19.8 per 100,000. (Irwin Law, personal communication) In an initiative of the government of Fiji to vaccinate young girls, a project to define HPV genotypes cervical cancer and CIN3 was undertaken in collaboration with Australian researchers.

In a cross-sectional analysis of archival cervical cancer and CIN3 biopsy samples from 296, overall 99% of the specimens tested were HPV DNA positive for high-risk genotypes, with detection rates of 100%, 97.4%, and 100% in CIN3, squamous cell carcinoma (SCC), and adenosquamous carcinoma biopsies, respectively. Genotypes 16 and 18 were the most common (77%), followed by HPV 31 (4.3%). Genotype HPV 16 was the most common identified (59%) in CIN3 specimens, followed by HPV 31 (9%) and HPV 52 (6.6% ; 34).

v) Sri Lanka
Recently reported a study from Sri Lanka, using archival cervical tissues (n = 108) from histologically proven SCC from 2006 to 2007 detected 93% of tumor samples as positive for HPV DNA, with HPV 16 and 18 accounting collectively for 83.4% (35).

These data defining genotyping in cancers from countries where no information has been available, supports the consistency of types 16 and 18 as being the dominant causes worldwide. They also provide baseline data, which one can compare the etiology of lesions postvaccination.

Conclusion
To quote from Elias A. Zerhouni, MD, Director, U.S. NIH

“It is the responsibility of those of us involved in today’s biomedical research enterprise to translate the remarkable scientific innovations we are witnessing into health gains for the nation.” (36)

We have the tools to markedly reduce HPV-related diseases globally, so let’s get on with it!

Disclosure of Potential Conflicts of Interest
S.M. Garland has honoraria from speakers bureau and is the consultant/advisory board member for CSL advisory board, GSK advisory board, GSK excel faculty. No potential conflicts of interest were disclosed by other authors.

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Conception and design: S.M. Garland, N. Bhatla, H.Y.S. Ngan
Development of methodology: S.M. Garland, H.Y.S. Ngan
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.M. Garland, H.Y.S. Ngan
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.M. Garland, H.Y.S. Ngan
Writing, review, and/or revision of the manuscript: S.M. Garland, N. Bhatla, H.Y.S. Ngan
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S.M. Garland, H.Y.S. Ngan
Study supervision: S.M. Garland, H.Y.S. Ngan

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