EXAMPLE 2.

HPV vaccination and screening for cervical cancer

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Introduction

Cervical cancer is a classic example of a preventable disease that causes significant morbidity and mortality in socially disadvantaged women, primarily because of inadequate access to universal health care. The disparities are further aggravated by sexual inequalities, which have a strong bearing on the health and rights of women and make them even more vulnerable (Singh et al., 2012). Cervical cancer is therefore a negative consequence of the systematic disadvantages that women experience as a result of social deprivation as well as sexual inequality.

Social inequality and cervical cancer burden

The imbalance in cervical cancer burden between the high-income countries (HICs) and low- and middle-income countries (LMICs) of the world highlights the lopsided access to preventive health care as a result of social and gender inequality. Pre-

vention of cervical cancer is one of the great success stories of modern medicine; the two-pronged approach of the vaccination of adolescent girls against human papillomavirus (HPV) and the systematic screening of adult women can potentially eliminate the disease (Tsu and Ginsburg, 2017). Despite this, cervical cancer continues to be the most common cancer in women in 27 countries and is the leading cause of cancer mortality in women in 45 countries, all LMICs (Fitzmaurice et al., 2015). IARC estimated that, in 2012, almost 90% of cervical cancer deaths occurred in LMICs, and there was an 18-fold difference between the highest and lowest mortality rates globally (Ferlay et al., 2013). Women with low socioeconomic status (SES) experience a higher burden of the disease. A pooled analysis based on 57 studies observed a globally increased risk of approximately 2-fold in groups of low versus high social class (by education and income) for the development of invasive cervical cancer (Parikh et al., 2003). The increased

risk exceeded 3-fold when the analysis was restricted to LMICs.

The mortality rates of cervical cancer are much higher in LMICs, because of the late-stage diagnosis of the disease and limited access to therapeutic services. A lack of awareness, a cultural preference for traditional healing systems over modern treatment, a lack of female empowerment, and the low priority of women's health in the family unit greatly contribute to delayed access to care (Denny et al., 2017). The plight of women with cervical cancer is worsened by the fact that only 50% of cancer patients in LMICs have access to radiotherapy, a much-needed treatment for cervical cancer (Zubizarreta et al., 2015). There are 28 countries in Africa without a single radiotherapy machine, and it is unlikely that the situation will improve in the near future (Abdel-Wahab et al., 2017). The social differentials that influence cervical cancer incidence and mortality also exist within HICs. Populations of racial and ethnic minorities encounter cultural barriers and prejudices

as well as financial hardship, leading to their underuse of health-care services. In the USA, African-American women experience 100% higher cervical cancer mortality rates compared with White women (10.1 per 100 000 vs 4.7 per 100 000 after correcting for hysterectomies; Beavis et al., 2017). The social costs of losing a wife and a mother at her prime to cervical cancer, and the hardships faced by the entire family because of the catastrophic health expenditure (e.g. children being forced to drop out of school), are greater for populations with low SES.

Indigenous populations and immigrants tend to have poorer access to health care, even in HICs. Their participation in cervical cancer screening programmes is often much lower compared with the rest of the population, for several reasons: poorly organized health services, political and economic marginalization, language barriers, and mistrust in modern health systems (Moore et al., 2014; Bianco et al., 2017). During 2003–2006, the age-standardized cervical cancer mortality rate for Indigenous women aged 20–69 years in certain provinces in Australia was reported as 10.3 per 100 000 women, 5 times as high as the rate of 2.0 per 100 000 for non-Indigenous women of the same age range (Australian Institute of Health and Welfare, 2009). The low participation in screening programmes by Indigenous women is the most significant factor contributing to this disparity.

Access to cervical cancer screening

The effect of social inequality

Many HICs have achieved up to 80% reduction in cervical cancer incidence and mortality rates by systematically implementing population-based screening (Vaccarella et al., 2014; Denny, 2015; Vaccarella et al., 2016). More than 70% of eligible women residing in the 28 Member States of the European Union have access to population-based cervical cancer screening (Basu et al., 2018). The beneficiaries of such programmes undergo a suitable screening test every 3–5 years and have access to appropriate follow-up care. This is in stark contrast to LMICs, including Baltic and eastern European countries, where cervical cancer screening either is non-existent or is provided in a highly sporadic manner, with poor-quality services and/or low coverage of the target population; consequently, cervical cancer rates are still rising in these countries (Vaccarella et al., 2016). The fragmented nature of health services, the lower priority of preventive health care, inefficient governance, inadequate resources, and competing health priorities preclude the implementation of well-organized screening programmes in LMICs (Denny, 2015).

Health-care financing models based on insurance can introduce inequalities within a country, because health-care needs are greater among those with the least ability to pay. Although extreme poverty in China has declined, rural elderly women have limited access to health facilities, especially preventive services, and are therefore victims of inequality (Tsu and Levin, 2008).

Closing the divide

For cervical cancer screening to become a reality in LMICs, an affordable, highly sensitive, robust, and point-of-care screening test is required, so that infrequent screening (once or twice in a lifetime) has a high impact and a minimum number of visits is required to manage screen-positive women. As described in Chapter 16, simple and inexpensive screening algorithms such as screening by visual inspection with acetic acid, followed by immediate treatment of eligible screen-positive women by cryotherapy, have enabled many low-income countries to implement cervical cancer screening and thus reduce inequality.

Cervical cancer screening programmes in LMICs should aim to screen women less frequently and achieve a high coverage of the target population. The test and the management algorithm should be selected depending on the health system capacity and available resources. It is imperative that health authorities address the structural, economic, and cultural barriers that women of remote, Indigenous, and immigrant populations face in accessing screening and treatment services. Some of the strategies to improve screening uptake in marginalized women include working closely with target groups, while involving key religious and community leaders, to develop culturally tailored messages to promote screening that reflect the values and beliefs of the target groups. A randomized controlled study demonstrated significant improvement in screening participation in Indigenous women in Canada by replacing the conventional Pap smear test with HPV self-testing (Zehbe et al., 2016).

Access to HPV vaccination

The effect of social inequality

Administering two doses of the HPV vaccine to preadolescent girls (aged

Fig. E2.1. Global map delineating the status of human papillomavirus (HPV) vaccine introduction in national immunization programmes (WHO, 2018). Partial introductions: Georgia, India, Indonesia, the Philippines, the Russian Federation, and the United Arab Emirates; planned introductions for 2018: Ethiopia, Grenada, Maldives, Mauritania, Saint Kitts and Nevis, and Senegal. Source: compiled from WHO/IVB Database.

- ■ Introduced (Includes partial introduction) to date (96 countries or 49%)
- □ Not Available, Not Introduced/No Plans (98 countries or 51%)
- ▨ Not applicable

9–13 years), with high coverage of the target population, is the most potent long-term solution to inequality in the cervical cancer burden. Rapid and significant declines in the prevalence of vaccine-targeted HPV infections, as well as in the prevalence of high-grade cervical premalignant lesions, at the population level after the introduction of the vaccine in the national immunization programmes have been reported by several countries (Gertig et al., 2013; Kavanagh et al., 2014). The excellent safety profile of the vaccine has been endorsed by the World Health Organization (WHO) and other vaccine surveillance agencies (WHO, 2017).

However, there remains a huge unmet need for HPV vaccination. According to the WHO database (updated in October 2018), a total of 91 countries (including 6 countries with partial introduction) now include the HPV vaccine in the national im-

munization programmes (Fig. E2.1) (WHO, 2018). Unfortunately, these include only 20% of the LMICs. Only three low-income countries (Rwanda, Uganda, and Zimbabwe) have included the vaccine in national programmes. It has been estimated that by 2014 only 32.0% of girls aged 10–14 years in HICs had received at least one dose of the vaccine; this proportion was only 15.2% in upper-middle-income countries, 0.2% in lower-middle-income countries, and 1.0% in low-income countries (Bruni, 2017). Because of the very low uptake of HPV vaccination before 2014 in the 72 low-income countries that were eligible to receive vaccine donations from Gavi, the Vaccine Alliance (previously known as the Global Alliance for Vaccines and Immunisation), only 2000 of the 400 000 potentially preventable cases of cervical cancer were averted (Jit et al., 2014). There are several

reasons to explain the low uptake of the vaccine, especially in LMICs: its high cost and competing health-care priorities, cultural issues related to a sex-specific vaccine, the logistical challenges of delivering a multidose vaccine and reaching adolescent girls, and the negative campaigns against the vaccine by the anti-vaccine lobbies.

Closing the divide

The high cost of the HPV vaccine has been a major impediment to its widespread introduction in LMICs. Price negotiations with the manufacturers by Gavi, the Vaccine Alliance (which negotiated a price of US$ 4.50 per dose for Gavi-eligible countries), the Pan American Health Organization Revolving Fund (which negotiated a price of US$ 9.58 per dose for Latin American countries), and national governments have drastically reduced the price. Pilot

vaccination projects are under way in 25 LMICs; many of these countries will scale up their programmes in the near future.

It is encouraging to note that the majority of HPV vaccination programmes in LMICs have achieved excellent target population coverage. Coverage was estimated for HPV vaccine demonstration projects and national programmes in 41 LMICs (Gallagher et al., 2017); final-dose (second or third dose, depending on the vaccination protocol) coverage estimates exceeded 50% in all 41 LMICs and exceeded 90% in nearly half of the LMICs. Interestingly, the reported HPV vaccine uptake among Indigenous girls has been high and comparable to that of non-Indigenous girls in countries where the vaccine is available through national immunization programmes (Brotherton et al., 2013; Jacobs-Wingo et al., 2017).

The reason for the success story of HPV vaccination in LMICs was the adequate preparation carried out before the launch of the programmes. Such preparation involved: adequately sensitizing national-level stakeholders, community leaders, and parents of eligible girls; coordinating with the education sector for school-based vaccinations; allowing sufficient time and resources for the planning process; and leveraging the existing logistics of routine immunization programmes. Higher coverage was achieved through school-based vaccination compared with health-facility-based vaccination (Paul and Fabio, 2014). Eligibility criteria based on school grade, rather than age, were more convenient to implement in school settings. However, these school-based programmes excluded girls who did not attend schools, thereby increasing social disparities among girls. A dual approach of school-based and health-facility-based vaccination can reduce this disparity.

Conclusions

The Seventieth World Health Assembly in 2017 endorsed vaccinating girls against HPV and screening women as the "best buy" to prevent cervical cancer. There is no dearth of evidence that a combination of vaccination and screening can potentially eliminate cervical cancer; the crux of the problem remains the socioeconomic disparities that preclude universal access to these preventive interventions. The education and empowerment of women, as well as improved access to reproductive health care and general increase in SES, have resulted in a slow decline in cervical cancer incidence in many LMICs, even in the absence of effective screening programmes. However, the impact of such social vaccination (prevention due to social changes) is limited, and may be offset by changing sexual practices. High coverage of the HPV vaccination and a pragmatic approach to ensure low-frequency but high-quality screening of vaccinated women can, in the long run, significantly reduce the disparity in the disease burden. It is the responsibility of national governments, political leaders, civil societies, and advocates to support the prevention of cervical cancer. Policies aimed at minimizing inequalities in health, reforming primary health care, pragmatically mobilizing resources, and prioritizing evidence-based and resource-appropriate interventions are key to preventing cervical cancer. Support from the global community can help to ensure that LMICs achieve their Sustainable Development Goals by preventing avoidable cervical cancer deaths.

References

Abdel-Wahab M, Zubizarreta E, Polo A, Meghzifene A (2017). Improving quality and access to radiation therapy-an IAEA perspective Semin Radiat Oncol. 27(2):109–17. https://doi.org/10.1016/j.semradonc.2016.11.001 PMID:28325236

Australian Institute of Health and Welfare (2009). Cervical screening in Australia 2006–2007. Canberra, Australia: Australian Institute of Health and Welfare. Available from: https://www.aihw.gov.au/reports/cancer-screening/cervical-screening-australia-2006-2007/contents/summary.

Basu P, Ponti A, Anttila A, Ronco G, Senore C, Vale DB, et al. (2018). Status of implementation and organization of cancer screening in the European Union Member States – summary results from the second European screening report. Int J Cancer. 142(1):44–56. https://doi.org/10.1002/ijc.31043 PMID:28940326

Beavis A, Gravitt PE, Rositch AF (2017). Hysterectomy-corrected cervical cancer mortality rates reveal a larger racial disparity in the United States. Cancer. 123:1044–50. https://doi.org/10.1002/cncr.30507 PMID:28112816

Bianco A, Larosa E, Pileggi C, Nobile CGA, Pavia M (2017). Cervical and breast cancer screening participation and utilisation of maternal health services: a cross-sectional study among immigrant women in southern Italy. BMJ Open. 7(10):e016306. https://doi.org/10.1136/bmjopen-2017-016306 PMID:29038177

Brotherton JM, Murray SL, Hall MA, Andrewartha LK, Banks CA, Meijer D, et al. (2013). Human papillomavirus vaccine coverage among female Australian adolescents: success of the school-based approach. Med J Aust. 199(9):614–7. https://doi.org/10.5694/mja13.10272 PMID:24182228

Bruni L (2017). Global vaccine uptake and projected cervical cancer disease reductions. HPV World. Newsletter on Human Papillomavirus. 1:6–9.

Denny L (2015). Control of cancer of the cervix in low- and middle-income countries. Ann Surg Oncol. 22(3):728–33. https://doi.org/10.1245/s10434-014-4344-8 PMID:25605513

Denny L, de Sanjose S, Mutebi M, Anderson BO, Kim J, Jeronimo J, et al. (2017). Interventions to close the divide for women with breast and cervical cancer between low-income and middle-income countries and high-income countries. Lancet. 389(10071):861–70. https://doi.org/10.1016/S0140-6736(16)31795-0 PMID:27814963

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. (2013). GLOBOCAN 2012 v1.0, Cancer incidence and mortality worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer.

Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF, et al.; Global Burden of Disease Cancer Collaboration (2015). The global burden of cancer 2013. JAMA Oncol. 1(4):505–27. https://doi.org/10.1001/jamaoncol.2015.0735 PMID:26181261

Gallagher KE, Howard N, Kabakama S, Mounier-Jack S, Burchett HED, LaMontagne DS, et al. (2017). Human papillomavirus (HPV) vaccine coverage achievements in low and middle-income countries 2007-2016. Papillomavirus Res. 4:72–8. https://doi.org/10.1016/j.pvr.2017.09.001 PMID:29179873

Gertig DM, Brotherton JM, Budd AC, Drennan K, Chappell G, Saville AM (2013). Impact of a population-based HPV vaccination program on cervical abnormalities: a data linkage study. BMC Med. 11(1):227. https://doi.org/10.1186/1741-7015-11-227 PMID:24148310

Jacobs-Wingo JL, Jim CC, Groom AV (2017). Human papillomavirus vaccine uptake: increase for American Indian adolescents, 2013-2015. Am J Prev Med. 53(2):162–8. https://doi.org/10.1016/j.amepre.2017.01.024 PMID:28256284

Jit M, Brisson M, Portnoy A, Hutubessy R (2014). Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study. Lancet Glob Health. 2(7):e406–14. https://doi.org/10.1016/S2214-109X(14)70237-2 PMID:25103394

Kavanagh K, Pollock KG, Potts A, Love J, Cuschieri K, Cubie H, et al. (2014). Introduction and sustained high coverage of the HPV bivalent vaccine leads to a reduction in prevalence of HPV 16/18 and closely related HPV types. Br J Cancer. 110(11):2804–11. https://doi.org/10.1038/bjc.2014.198 PMID:24736582

Moore SP, Forman D, Piñeros M, Fernández SM, de Oliveira Santos M, Bray F (2014). Cancer in indigenous people in Latin America and the Caribbean: a review. Cancer Med. 3(1):70–80. https://doi.org/10.1002/cam4.134 PMID:24403278

Parikh S, Brennan P, Boffetta P (2003). Meta-analysis of social inequality and the risk of cervical cancer. Int J Cancer. 105(5):687–91. https://doi.org/10.1002/ijc.11141 PMID:12740919

Paul P, Fabio A (2014). Literature review of HPV vaccine delivery strategies: considerations for school- and non-school based immunization program. Vaccine. 32(3):320–6. https://doi.org/10.1016/j.vaccine.2013.11.070

Singh GK, Azuine RE, Siahpush M (2012). Global inequalities in cervical cancer incidence and mortality are linked to deprivation, low socioeconomic status, and human development. Int J MCH AIDS. 1(1):17–30. https://doi.org/10.21106/ijma.12 PMID:27621956

Tsu VD, Ginsburg O (2017). The investment case for cervical cancer elimination. Int J Gynaecol Obstet. 138(Suppl 1):69–73. https://doi.org/10.1002/ijgo.12193 PMID:28691328

Tsu VD, Levin CE (2008). Making the case for cervical cancer prevention: what about equity? Reprod Health Matters. 16(32):104–12. https://doi.org/10.1016/S0968-8080(08)32411-2 PMID:19027628

Vaccarella S, Franceschi S, Bray F (2016). The incremental benefits of implementing effective cervical cancer screening. Int J Cancer. 138(1):254–5. https://doi.org/10.1002/ijc.29700 PMID:26205613

Vaccarella S, Franceschi S, Engholm G, Lönnberg S, Khan S, Bray F (2014). 50 years of screening in the Nordic countries: quantifying the effects on cervical cancer incidence. Br J Cancer. 111(5):965–9. https://doi.org/10.1038/bjc.2014.362 PMID:24992581

Vaccarella S, Franceschi S, Zaridze D, Poljak M, Veerus P, Plummer M, et al. (2016). Preventable fractions of cervical cancer via effective screening in six Baltic, central, and eastern European countries 2017-40: a population-based study. Lancet Oncol. 17(10):1445–52. https://doi.org/10.1016/S1470-2045(16)30275-3 PMID:27567054

WHO (2017). Immunization, vaccines and biologicals: human papillomavirus (HPV). World Health Organization. Available from: http://www.who.int/immunization/diseases/hpv/en/.

WHO (2018). Vaccine in national immunization programme update. World Health Organization. Available from: http://www.who.int/entity/immunization/monitoring_surveillance/VaccineIntroStatus.pptx.

Zehbe I, Jackson R, Wood B, Weaver B, Escott N, Severini A, et al. (2016). Community-randomised controlled trial embedded in the Anishinaabek Cervical Cancer Screening Study: human papillomavirus self-sampling versus Papanicolaou cytology. BMJ Open. 6(10):e011754. https://doi.org/10.1136/bmjopen-2016-011754 PMID:27855089

Zubizarreta EH, Fidarova E, Healy B, Rosenblatt E (2015). Need for radiotherapy in low and middle income countries – the silent crisis continues. Clin Oncol (R Coll Radiol). 27(2):107–14. https://doi.org/10.1016/j.clon.2014.10.006 PMID:25455407