GUEST EDITORIAL

AFFORDABILITY OF HPV VACCINE IN DEVELOPING COUNTRIES

Sharifa Ezat WP[1], Syed MA[2]

[1]Dept of Community Health, Faculty of Medicine, National University of Malaysia Medical Centre
[2]United Nations University-International Institute for Global Health

INTRODUCTION

Malaysia health care system

Malaysia has an efficient and widespread system of health care[1] (MOH, 2006, WHO 2008, Chai et al, 2008). It provides quality, equitable, and cost effective care to its people (WHO, 2006; MOH, 2006). As a result, Malaysia fares favorably on many of the standard health indicators. The infant mortality rate in 2007, at 6.3 per 1000 live births, is a strong indication of the overall efficiency of healthcare in this country. Life expectancy at birth in 2007 was 74.1 years. These achievements led to an improved Malaysians Quality of Life Index[2] (MQLI) which increased from 110.93 (2004) to 117.33 (2006). Overall health index i.e. health aspects pertaining to physical and mental well being, increased as well from 118.10 in 2004 to 130.74 in 2006 (Ministry of Finance, 2008). Malaysia has achieved nearly universal access to health care. According to the MOH[1], basic health amenities are available to more than 93% of the population of East Malaysia and are accessible within 5 kilometres[3]. However, the coverage is lower for the states of Sabah and Sarawak in West Malaysia at 76 percent and 61 percent respectively although the health facilities are accessible within 3 km (Annual Report MOH, 2006). In achieving the Vision for Health and Mission of the Ministry of Health, the activities carried out by the health sector must be in line with the eight goals of the health services: wellness; person-focused; informed person; self-help; care provided at home or closer to home; seamless, continuous care; services tailored to individual or group needs; and effective, efficient and affordable services.

The public health services are divided into hospital and primary health care sectors (MOH, 2006). The hospital sector offers primary health care through district based hospitals and secondary hospitals that provide limited specialist services. These will include minor operation theatres (OT) procedures; lab investigations, routine interventions or treatments. At this level, patients who require highly intensive interventions will be referred to higher level facilities that are located in urban areas and cities. They are more equipped and supported by blood banks, operations theatres and higher intensity equipments and technology.

Not surprisingly, the rapid economic growth in Malaysia led to a growing presence and role of the private health care system which offers an extensive menu of promotive, preventive and curative services. The system, mostly available in urban areas, consists of general practitioners in small clinics to private hospitals up to 2000 beds. Private health care is covered directly by the patients through out of pocket or through private health insurance whose premiums are based on individual's risks. Given the voluntary high premiums, only a total of 18.8 percent of Malaysians can afford private health insurance[3] (National Health Morbidity Survey 2006, MOH, 2006).

Perceived to be of high quality, those who can afford to pay prefer private health care services. The perceived quality in the private sector is difficult to determine due to insufficient data[4] (WHO 2006). Lured by better salaries and incomes, experienced and skilled health professionals have joined the private sector which poses a challenge for the public sector. In 2000, 54 per cent of doctors in the public system had to care for 80 per cent of patients nationwide[5] (Dato' Liow Tiong Lai, NST 12th July 2010). The remaining 46 per cent of doctors are in the private sector, but they only had to contend with 20 per cent of patients in the country. Sixty per cent of specialists in the country are in the private sector, but they only look after 25 per cent of the most complicated cases.

Malaysia's policy and implementation of the Expanded Program for Immunization (EPI) is a very

strong commitment and achievement[1,4]. The coverage of childhood vaccination showed that coverage is almost more than 90% in all areas even the rural areas. The mechanisms of delivery include the subsidized school health teams (under the MOH school health programs); private health facilities example from general physicians, other ministries, and public health centres.

PROBLEM ANALYSIS

Malaysia is experiencing a challenging epidemiological transition where both communicable and non communicable diseases are considered high disease burdens. Sedentary lifestyles, poor eating habits and risky behaviours resulted in the following leading disease burden based on disability-adjusted life years (DALYs) [5](Malaysian Burden of Disease and Injury Study Report, MOH 2004): (1) among Males: ischaemic heart disease, road traffic accidents, cerebrovascular diseases, septicaemia, and acute low respiratory tract infections; and (2) among Females: ischaemic heart disease, cerebrovascular disease, unipolar major depression, septicaemia and diabetes.

World-wide, cervical cancer is second only to breast cancer as the most common female malignancy in both incidence and mortality. More than 80% of new cases are diagnosed in economically disadvantaged people. Singapore Cancer Registry[6] (Seow et al 1992) indicated that the age-standardized incidence of cervical cancer has decreased from 18.2 per 100,000 females in 1968-72 to 16.2 per 100,000 in 1983-87, and its ranking among the most common female cancers had fallen from second to fourth place behind cancers of the breast, colon, rectum and lung. Mortality from the disease had also shown a corresponding fall from 7.3 per 100,000 to 5.5 per 100,000 women over the same period. The second report of Malaysian National Cancer Registry[7] (2003) showed that the ASR of cervical cancer in Malaysia is 19.7 per 100,000 populations.

The newest age standardized rate of cervical cancer among Malaysian Chinese was 23.2 per 100,000 population and Indians 16.4. These figures are higher than the Singaporean Chinese (15.0) and Indians (8.2)[8] (National Cancer Registry 2003-2005). The incidence among Malays in Singapore (9.9) was comparable to that in Malaysia (8.7). By morphology of cases, SCC (71.7%) was the predominant morphology found, followed by adenocarcinoma (18.9%).

Age-specific incidence curves over time showed a marked fall in rates in women over 50 years of age, whereas younger women (35-44 years old) showed a small increase. A similar increase in rates had been observed in various other countries. Internationally, Singapore's incidence rate had fallen between that of South America and parts of Asia, and the lower rates of North America and Europe. The decrease in rates was comparable with the overall global trend, but fell short of that achieved by countries with systematic cytological screening programs with many coming in at late stages of diseases.

Cervical cancer is an important reason for hospital admission. This is consistent with the Malaysian National Cancer Registry Report[7] (2003) that found that the most frequently occurring cancers in Malaysian women were cancers of the breast, cervix and colorectal cancer in that order. The Penang Cancer Registry 1999-2003 showed that 29.3% of cases presented at stage 1, 40.0% at stage 2, 23.9% at stage 3 and 6.8% at stage 4[9] (Penang Cancer Registry 2004). This figures indicated that many women was referred in stage 2, then stage 1, 3 and lastly in stage 4. This is a relatively late referral whereby detection was late and disease has progressed to a more advanced stage. The second report of Malaysian National Cancer Registry (2003) showed that the risk of cancer of the cervix in Malaysian ASR of 19.7 for 100,000 populations was higher compared to other Asian countries and Western countries.

The Malaysian Clinical Practice Guideline 2003[10] and Guidebook for Pap smear screening, M0H[11] (2004) recommended that all women who are sexually, or who has been sexually active, between the ages of 20 and 65 years, to undergo Pap smear testing. If the first two consecutive Pap smear results are negative, screening every three years is recommended. Even though the regime is somewhat standard, the opportunistic nature without an established call recall system, many women are lost to follow ups and do not return for further appointments. Another cost effective strategy through Visual Inspection with Acetic Acid (VIA) advocated by WHO, is another strategy that

the nation are considering at. The move would to be able to implement real time detection and catching early cancer at a speedier pace.

HPV vaccine research is being led by two pharmaceutical giants, Glaxo Smith Kline (GSK) and Merck & Co (in United States; elsewhere as Merck Sharp & Dohme or MSD) with each having developed first generation prophylactic vaccines[12,13,14] (Koutsky et al. 2002, Harper et al 2006, Joura et al 2007) with successfully registering it for use since 2006. Potential vaccines will target HPV 16 and 18 and cross infection protections against multiple HPV types such as types 31, 33 and 45. There is evidence of cross protection depending on the antigens used for immunization (Rousseau et al 2001) but it ranges from minimal to as high as 45%. Merck's L1 virus like particle (VLP) vaccine is based on recombinant yeast technology designed to protect both males and females against HPV types 16 and 18 (highly oncogenic types or high risks) as well as HPV types 6 and 11 (low risk), so called the quadrivalent vaccine (QV). The former pair has associated with cervical cancer while the latter causing genital warts. Although most HPV infections are benign, persistent infection (repeated detection of an oncogenic type of HPV) is associated with the development of cervical cancer after a decade or so [14](Joura et al 2007). GSK's bivalent vaccine (BV) is based on the recombinant baculovirus technology and formulated with the proprietary adjuvant Aluminum Sulphate 04 (AS04) but prophylaxes are only against HPV types 16 and 18. Both vaccines are considered safe and effective in producing response greater than natural infection; no established serious side effects that were significantly differed from the control populations and both had evidence of different levels of cross protection[12,13](Ault 2006, Harper et al 2006). The vaccines will need three intramuscular administered doses given in between the duration between 0-6 months to be fully effective.

The high incidence of cervical cancer prompts Malaysia to put HPV vaccination as the high priority for adolescents' vaccination program through the SHP among adolescent girls in the country. The delivery method will be through the school health program (SHP) and its team, where delivery will be systematically covering all public schools. Private schools that the SHP team do not cover; meant that the adolescents' girls will have to purchase the HPV vaccine from the private health providers or obtain the vaccination at the nearest public health centres of their parents' choices. However, the purchase prices of these vaccines are relatively high to be borne out of pocket and most parents will hesitate to purchase these vaccines at their own cost. Malaysia has ensured universal coverage for its population and ensuring childhood vaccination to be considered a public good to the population, making it free of charges and available at health centres. The ability of vaccination delivery and administration by nurses at schools is also a prominent strength for Malaysia to ensure childhood vaccinations are continued at the primary and secondary school level.

Options in financing vaccination programs

The HPV vaccine is one of the newer generation EPI vaccines, other vaccines in these category would include the pneumococcal vaccine and Rotavirus vaccines. It entails a high cost to produce, store and administer as three intramuscular doses are needed for each girl[15]. Secondary to the high cost, it represents a major hurdle towards mass vaccinations on adolescent girls. Based on the UNICEF category, Malaysia is considered to be in the band C category. Band C countries are supposedly to be self sufficient and are no longer eligible for donor assistance. We are also encouraged to procure new vaccines through direct negotiation with manufacturers.

Developed countries with high income and resources would not face a major obstacle in mass implementation and rollout in countries that has an established financing and delivery system of EPI. However in developing and under developed nations; high cost of mass vaccine purchase and administration among its adolescent's girls becomes an almost impossible feat. This is even if they receive one-off or ad-hoc seed money from donor organizations; most of these activities would become unsustainable in the long run. The irony is that these are the countries urgently needing cervical cancer prevention in the form of mass HPV vaccination; as the cervical cancer screening programs are usually underfunded, under resourced, less established and opportunistic in nature. The adolescents' girls that makes up the population pyramid of under developed and developing countries make up a huge proportion of its women, and future incidences and prevailing cervical cancer in these girls cohort would impose a

major economic burden to these countries. In order for novel vaccines to become off patent, the time would be between a decade or two.

The Global Alliance for Vaccines and Immunization (GAVI)[15] was formed in 1999 to "re-energize the world's commitment to vaccines and immunization." GAVI is a coalition of public- and private sector partners including national governments, WHO, UNICEF, the World Bank Group, the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) and the Bill and Melinda Gates Foundation.

Underdeveloped countries that ultimately satisfy the Global Alliance for Vaccines and Immunization (GAVI) board and eligibility criteria would be potential supported with external funding to support purchase and immunization activities. Countries with less than USD1000 GDP per capita and immunization coverage of less than 80% are eligible to apply, though applying countries need to propose criteria to ensure sustainability and successful running of programs. The main two producers of HPV vaccines are committed to reduce selling prices to under developed countries and if the bulk of purchase would be enough to support mass productions and economy of scale purchases. With long term target for market demand, more suppliers would come in and market value may come down to probably marginal cost. Another method in financing HPV vaccines with developing countries, a mechanism that is worth mentioning is the 'Advanced Market Commitment' (AMC)[16]. The AMC concept is dependent on donors (donor agencies such as Bill & Melinda Gates Foundation and developed countries) that could commit to subsidize the purchase and development of new vaccines demanded by developing countries. This predetermined amount of money to pharmaceutical companies acts as an incentive to produce vaccines. This commitment would present as an added value to entice private sectors to invest in vaccination commitment as well. These large scale demands by countries are expected to reduce prices of new vaccines including HPV vaccine sooner than the market naturally could. The six potential vaccines targeted are against rotavirus (causes diarrhoea), pneumococcal pneumonia (causes respiratory disease), HPV, malaria, tuberculosis and HIV/AIDS. Not without its own flaws and critics, AMC is not a magic tool and the end prices that they target (halve the prices of the six vaccines) are doubtful. For middle income developing countries, there is a need to build their own financing capacity to purchase to run these programs on a sustainable course. Projections of future demand by the population are routinely implemented by pharmaceutical companies including GSK and Merck[15]. Manufacturers need to be assured that demand is there and financing is secured in order to scale up demand to meet developing country markets. These studies[18] must also be incorporated into population based modeling of future trends of disease burden and its impact on national budget. These methods of budget impact assessments tools are essential in predicting cost and costs that could be potentially saved from health intended interventions on the population. At the country's level, the government i.e. the Ministry of Finance, Education and Health must be convinced of the benefit of the HPV vaccinations programs have on the adolescents and women in the future. Local data on cost effectiveness (CE) studies presented to the government will prove the HPV vaccines are indeed cost effective and are a long term investment to the country and its women. As many middle income countries have better health fiscal space; private health providers play a role to provide HPV vaccinations at a predetermined user fees charges. The upper scale population is able to tap into the private providers but these vaccines provisions are relatively small in coverage. However the vaccine early entry into the private sectors had created an early buzz among the medical fraternity, among potential consumers, creating awareness of the vaccine arrival and its potential benefits.

Policy implementation of HPV vaccination

The impact of many cost effective (CE) studies[16,17] done in Malaysia had catapult many vaccination programs to be put into the existing EPI program. Such an example would be the previously implemented traditional HIB vaccination program, HPV vaccination program and the near future pneumococcal vaccination program. Besides health technology assessments such as CE studies advocated by WHO and NICE; the governments' commitment to bring forth the best interventions and services to its community must be applauded, but also maintained in the future settings. Approaches through economic evaluations techniques such as CE studies, cost effectiveness studies and budget impact assessments had put HPV vaccination program into the nations existing

EPI implemented since 2010 with an initial budget of 150 million[18].

CONCLUSION

Methods of vaccination programs vary across regions and financial capability of different countries. Local pharmacoeconomic researches done at country specific levels reduce doubt of the benefits of HPV vaccines or other novel vaccines that are approaching the pharmaceutical markets. Private health sectors play a role in advocating HPV vaccines implementation in middle income countries albeit the low coverage among population with the ability to pay for such schemes.

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