

National Immunization Summit 2015

16th January, 2015 Colombo, Sri Lanka

The 3rd National Immunization Summit organized by the Epidemiology Unit of the Ministry of Health was held at the Hotel Cinnamon Grand Colombo, on 16th January, 2015.

Many participants representing all relevant authorities of the Ministry of Health, Professional Colleges, Academic institutions including Universities, UN organizations, and other experts of various fields had actively involved in discussions. Few participants from interested parties attended as passive observers. Dr. Krisantha Weerasuriya acted as the moderator of the summit.

Current themes of importance were selected as follows for the discussion with evidence based information and presented by the Epidemiology unit. Each theme was opened for a discussion for effective decision making after each presentation.

Introduction of inactivated Polio Vaccine (IPV)	Dr. Paba Palihawadana	Chief Epidemiologist
Sero-conversion status after single dose of live Japanese encephalitis vaccine (LJEV) Sri Lankan experience	Dr. Samitha Ginige	Consultant Epidemiologist
Cervical Cancer Burden and Options on HPV Vaccination	Dr. Deepa Gamage	Consultant Epidemiologist
Immunization in Pregnancy	Dr. Ananda Amarasinghe	Consultant Epidemiologist
Measles Immunity Status in Sri Lankan Population	Dr. Deepa Gamage	Consultant Epidemiologist
Invasive Bacterial Diseases Surveillance in Sri Lanka	Dr. Madhava Gunasekara	Senior Registrar in Community Medicine
Rota virus gastro-enteritis Surveillance in Sri Lanka	Dr. Madhava Gunasekara	Senior Registrar in Community Medicine
Hepatitis B seroprevalence survey Sri Lanka	Dr. Jagath Amarasekara	Consultant Epidemiologist

Introduction of inactivated Polio Vaccine (IPV)- Dr. PabaPalihawadana

History of the global and Sri Lankan Poliomyelitis situation and a long way to the current status was presented. It was highlighted that only Afghanistan, Pakistan and Nigeria were presently endemic and the programme is striving hard at the end stage of eradication. As Endgame strategies of Polio eradication, the requirement of (a) gradual shifting over from Oral Polio Vaccine (OPV) to Inactivated Polio Vaccine (IPV) and (b) travellers' vaccination were discussed.

Out of the 3 Wild Polio Viruses (WPV), only WPV 1 is at the transmission in polio endemic and other polio infected countries as imported cases. WPV type 3 is not seen for the last 2 years and still it is unable to declare as free from it but WPV type 2 is out of transmission since 1999.

OPV, live attenuated vaccine contains rare but serious side effects of Vaccine Associated Paralytic Poliomyelitis (VAPP) and evolution of Vaccine Derived Polio Virus (VDPV). Though WPV type 2 is not seen globally any more VDPV type 2 has caused few outbreaks in under immunized populations in some other countries. With such evidence now recommendations have been in place to withdraw type 2 from OPV and only bOPV including only Type 1 and 3 would be manufactured in future.

The strategy of shifting over from OPV to IPV will be in phasic manner identifying the requirement of maintenance of adequate gut immunity as well as protecting immunity levels for Type 2 polio virus.

1. 2015 May: IPV will be introduced as an additional dose while keeping with already existing National schedule.
2. Additional IPV dose will be introduced with the 2nd dose of Pentavalent vaccine and OPV vaccine
3. 2016: trivalent OPV (tOPV) in the current National Immunization schedule will be replaced with bivalent OPV (bOPV)
4. National schedule will include 4 doses of bOPV and one IPV dose
5. 2018 or later: with global recommendations, total shifting over to IPV from OPV will take place.

This rationale for changing the Polio vaccination schedule was discussed and cost implications to the programmes was talked over. It was explained as current vaccine requirement would receive with GAVI support for 4 years and then to be taken over under the EPI budget.

In this context, it was considered to identify the background population immunity levels for polio and seroprevalence survey carried out in 3 districts (Colombo- urban slums, Killinochchi-resettlement areas, Badulla-estate sector) among representative population age categories (9-11 months, 3-4 years, 7-9 years, and 14-15 years). Children in the selected age groups appeared to be sufficiently protected against all three poliovirus serotypes. This is true even for children coming from the lower socio-economic strata. Lower polio virus type 3 seroprevalence in the older age groups is likely due to waning of humoral immunity but cellular immunity would provide protection. No significant difference of antibody levels is found in each type between districts.

Sero-conversion status after single dose of live Japanese encephalitis vaccine (LJEV) Sri Lankan experience- Dr. Samitha Ginige

In Sri Lanka, Immunization against JE with the inactivated JE vaccine was introduced on a phased basis as a mass vaccination programme targeting high risk districts in 1988. In 2009 inactivated JE vaccine was replaced with Live JE vaccine (LJEV) . LJEV was introduced into the National Immunization schedule in 2011 as a routine vaccine covering the entire country. Before 2011 JE vaccination was limited to 18 high risk districts.

Since the introduction of vaccination against JE Sri Lanka has shown a steady decline in the incident of lab confirmed JE cases over the years (1985 JE incidence – 15 per 100000 pop to 0.1 per 100000 pop in 2014). In addition, currently around 70% of lab confirmed reported cases were among over 20 years old age groups which were not exposed to JE vaccination. All these evidence shows the effectiveness of vaccination against JE.

Compared to inactivated vaccine Live JE vaccine has;

- ❖ Simpler schedule (one or two doses compared to minimum of 4 doses of inactivated vaccine)
- ❖ Better safety profile (proven with National AEFI Surveillance data)
- ❖ Cheaper price (1US\$ to 4US\$ per dose)

Sri Lanka introduced single dose of LJEV at 9 months of age to EPI in 2009 based on;

- ❖ Findings of LJEV safety and immunogenicity study conducted by the Epidemiology unit in 2007 in the Colombo district with 257 subjects. This study revealed that 87% of subjects have protective antibody levels one year after a single dose of LJEV.
- ❖ Limited serological studies done in other JE endemic countries (Nepal, Thailand, Philippines, and Korea), too have revealed that a single dose of LJEV is capable of providing a protective antibody levels in majority of subjects. Most of those studies have relatively smaller sample size.
- ❖ WHO position paper on JE vaccination has (2006) mentioned "Good childhood protection is obtained by a single dose of the cell-culture based, live attenuated vaccine followed by a single booster given at an interval of about 1 year." The live attenuated vaccine induces protection for several years after **1 or 2** doses.
- ❖ Other Regional country experiences – Both India and Nepal use to give a single dose of LJEV. China is used to give 2 doses of LJEV at 8 months and 2 years of age.

- ❖ LJEV manufacturer has recommended as – "According to the available clinical data, Single primary dose of LJEV given at 8 months of age can provide protection up to 5 years. In some countries for programmatic purposes a booster dose at 2 years of age is recommended"
- ❖ It was decided to review the immunogenicity among vaccines five years following the introduction of LJEV into the Sri Lankan EPI.

In 2014 Epidemiology unit has done a JE sero prevalence study in Colombo, Kalutara, Puttalam and Anuradhapura districts with 500 subjects to assess the immunogenicity following a single dose of LJEV. This study has revealed that only 40% (CI 31 -48) of subjects have protective JE antibody levels (PRNT \geq 10) 1 year after LJEV. This figure was 29%, 2 and 3 years following LJEV. Geometric mean titer (GMT) for JE neutralizing antibodies shows steady decline over the years following single dose of LJEV (GMT -66 one year following LJEV, GMT – 22 five years following LJEV).

Current study reveals that a Single dose of LJEV did not provide adequate neutralizing antibody titers in majority of Sri Lankan study subjects over the years following vaccination. These findings somewhat differ from similar studies done in other JE endemic regional countries and similar study done in Sri Lanka, 7 years ago.

Limited available literature suggested that subjects who have failed to achieve adequate protection following a single dose of LJEV demonstrated a booster response with high GMT after the second dose of LJEV.

This issue was discussed at the National Immunization Summit 2015 and it was decided to introduce the second dose of LJEV to the National EPI. Timing of the second dose will be decided after considering the programme feasibility.

Cervical Cancer Burden and Options on Human Papilloma Virus (HPV) Vaccination- Dr. Deepa Gamage

Most of the HPV infections are asymptomatic and cleared within 2 years without any disease condition. If not cleared and persistent infections can lead to anogenital warts, recurrent respiratory papillomatosis (RRP), cervical cancer precursors (cervical intraepithelial neoplasia = CIN), cancers of cervical, anal, vaginal, vulval, penile and oropharyngeal.

There are more than 100 genotypes of HPV and around 40 types are associated with mucosal / genital infections which include high risk oncogenic and low risk non oncogenic genotypes. While majority of HPV infections are clearing about 10% of persistent HPV infections would lead to cervical cancers in 10-15 years.

Cervical cancer is the 2nd most common female cancer in Sri Lanka and according to most latest published data from National Cancer control Programme 10% of all female cancers are cervical cancers. Nearly 850-950 new cervical cancer cases are admitted to government hospitals calculated to crude incidence rate of 7.3/ 100,000 population in Sri Lanka. National Cancer Control Programme is piloting a “Population based cancer registry” in the district of Colombo since 2012 and feasibility assessments are underway.

Preventive options for cervical cancers are described as:

- Early detection and treatment of cervical cancers in cervical cancer screening and management of precancerous stages and invasive cervical cancer stages
- Vaccination : for prevention of genital HPV infection due to High Risk (HR) genotypes

Cervical cancer screening by doing Pap smear screening is carried out by the Family Health Bureau under the implementation of Well Women Programme since 1996 above the age of 35 years and the present coverage is around 30-40%.

The HPV community prevalence study done in the district of Gampaha in 2009 among 20-59 year old sample number of 2000 women showed overall prevalence of 3.3% (95% CI 3.2-3.4) while HR geno types 16 and 18 prevalence of 1.2% (95% CI 1.15-1.25). On genotype identification the majority were HR genotype 16 and 18 (42%).

The number needed to screen in prevention of one cervical cancer was estimated applying study findings of HPV infection status, pre-cancers and cervical cancers to the literature described cervical cancer progression proportions. It was estimated to 1130 when considered only above 35 year old women and described that nearly one million women need to be screened by Pap smear per year in prevention of total cervical cancer case load of 850-900 new cases.

A case control study to assess the HPV risk attribution in developing cervical cancer by studying 40 cervical cancer cases and 160 age category and area matched community controls showed HPV positivity rate of 80% among cases and 3.8% among controls. Population attributable risk percent (PAR%) has been calculated to 85% for all genotypes and 69% for HR geno type 16 and 18. This means that out of 100 cervical cancer cases 69 contributed by HPV genotypes 16 and 18 in Sri Lanka and compatible with 70% which is described in literature.

Preventive option of vaccination was discussed and the available 3 types of vaccines discussed as follows:

- Quadrivalent HPV (HPV4) vaccine (for prevention of 70% of cervical cancer cases)
 - Contains HPV types 16 and 18 (high risk) and types 6 and 11 (low risk)
 - Approved for females and males aged 9 through 26 years

- Bivalent HPV (HPV2) vaccine (for prevention of 70% of cervical cancer cases)
 - Contains HPV types 16 and 18 (high risk)
 - Approved for females aged 10 through 25 years

- Ninevalent HPV vaccine (9v HPV) (for prevention of 90% of cervical cancers)
Contains HPV geno types 6, 11, 16, 18, 31, 33, 45, 52, and 58 ,for use in girls and young women 9 to 26 years of age , for prevention of cervical, vulvar, vaginal, and anal cancers ,pre-cancerous or dysplastic lesions genital warts caused by HPV types 6 and 11.

Future areas which need strengthening in cervical cancer prevention was discussed as requirement of proper cervical cancer burden identification, expansion of cervical cancer screening and possible vaccination options considering cost prioritization preventive strategies. It was decided to form an expert committee to further discuss on this and provide observations to the Advisory Committee on Communicable Diseases.

Immunization in Pregnancy- Dr. Ananda Amarasinghe

Vaccination during pregnancy

An overview on use of vaccine in pregnancy was presented at the immunization summit and following areas were presented and discussed; (i) other country recommendations on use of vaccines in pregnancy (ii) obstacles to accurate assessment of risk of immunization in pregnancy and (iii) safety concerns in pregnancy with tetanus toxoid, rubella, measles and mumps containing vaccines, yellow fever vaccines and influenza vaccines

Risk to a developing foetus from vaccination of the mother during pregnancy is primarily theoretical. Although the use of most vaccines during pregnancy is not usually recommended on precautionary grounds, there is no convincing evidence that pregnancy should be an absolute contraindication to the use of any vaccine, particularly inactivated vaccines. As is common, clinical trials during vaccine development and licensure did not target pregnant women, however inadvertent vaccination in pregnancy throughout the early phases had not revealed any concerns.

It highlighted the potential obstacles to look at the safety of vaccines, especially in outcomes as complex as pregnancy; maternal, foetal and neonatal mortality and morbidities including spontaneous abortions, still births, perinatal deaths, prematurity, low birth weight, small for gestational age, and rates of congenital abnormalities. Absence of background rates of these adverse outcomes is a challenge to evaluate adverse events of vaccination during pregnancy.

Overall, available evidence in medical literature indicates that there are no concerns of vaccination in pregnancy. Both activated and inactivated vaccines have not indicated increased safety risk for adverse reactions/events during pregnancy including any trimester.

The conclusions are;

- Pregnancy is 'routinely' exclusion criteria in vaccine pre-licensure human studies. Therefore, manufacturers list pregnancy as contra-indication due to non availability /lack of evidence and as a pure precautionary measure.
- The available data (based on vaccine pre-licensure animal studies or post-licensure studies) on vaccination in pregnancy have not shown evidence to indicate the occurrence of foetal, infant and maternal adverse effects, susceptible of being attributed to the vaccine.
- The benefits of vaccination outweigh the potential 'theoretical risks' used in pregnancy, particularly when the burden of disease is high and, need attention in decision making.
- Inadvertent vaccination (particularly with live vaccines/rubella containing vaccine) during pregnancy does not indicate termination of pregnancy
- Robust safety profile and the benefits of influenza vaccination to the mother and newborn have been demonstrated for both seasonal influenza and influenza pandemics. Therefore, WHO recommends influenza (inactivated vaccine) vaccination during pregnancy

Measles Immunity Status in Sri Lankan Population-Dr.DeepaGamage

In 1982, Sri Lanka has experienced an outbreak situation and surveillance activities were strengthened. Implementation of measles vaccination at the age of 9 months has been started in 1984/85 and experienced a marked case load reduction (incidence of 0.5/100,000 population) by 1998.

But the country has experienced periodic sporadic outbreaks from time to time and during 1999-2000 experienced a massive outbreak with >20,000 cases with around 200 deaths which led to the decision of introduction of a second dose of Measles Containing Vaccine (MR) at the age of 3 years in 2001. Catch-up campaigns were conducted among 10-14 year age group in 2003 with 95% vaccination coverage and among 16-20 year age group in 2004 with 72% vaccination coverage.

The National schedule has been changed with very low measles transmission status in the country in 2011 by changing over from measles and MR to MMR and 9 months measles dose advanced over to 1 year of age. In 2013-2014 a measles outbreak situation was experienced in the country with an increased case load of around 5000 cases. Possible impact of global other country outbreak situations during 2013-2014 for high transmission situation in the country was described but recognized the issues of possible immunity gaps in the population and requirement of laboratory confirmation of all cases in case based investigations at the elimination stage. Epigraph with age category distribution in outbreak situation showed higher proportions among infants.

Since the country maintained very high MMR vaccination coverage in the National schedule at the age of 1 and 3 years even at district level, and the country is experiencing an outbreak situation, while planning to achieve elimination target of <1 case / million population by 2020, a seroprevalence study was carried out to identify population immunity levels in different age categories (6-8months , 9-11 months, 2 years, 5 years, 15-16 years, 20-29 years and 30-39 years) in randomly selected 4 districts among 800 persons.

Measles IgG antibody levels showed 95% protective level among vaccinated and non protective antibody levels among age categories of 6-8months (94%) and 9-11 months (99%). All other age groups were with high protective population proportions. Mean and median population immunity titres at each age categories showed well above the protective antibody level indicating population immunity well maintained between 2-40 year age group. Infants 6 months to 1 year are not protected for measles and explains with the evidence from other countries that antibodies of babies of vaccinated mothers would wane earlier than the antibodies in babies of naturally infected mothers with measles.

Reviewing countries which used MMR below 1 year identified Germany, France, Thailand and Bahamas included in the National schedule and recommended to use for travellers and/or used in supplementary activities in England Wales and USA.

Decided to change the vaccination schedule and change the MMR implementation lowest age category to 9 months for the benefit of infants in protecting them.

Invasive Bacterial Diseases Surveillance in Sri Lanka-Dr.Madhava Gunasekara

Before widespread immunization, annual incidence of Invasive Pneumococcal Diseases (IPD) in children aged <2 years was

- 44.4/100 000 per year, in Europe
- 167/100 000 per year, in the United States
- 60/100 000 per year, in South Africa
- 797/100 000 per year, in Mozambique

On average, about 75% of Invasive Pneumococcal Disease cases and 83% of pneumococcal meningitis occur in children aged <2 years (WHO).

Hospital based IBD surveillance started in 2009 and continuing at the Lady Ridgeway Hospital, Colombo with the assistance of World Health Organization. During this period (2009-2014), a total of 3305 children (age 0-59 months) were enrolled in the study.

The objective of this special surveillance project is to assess the burden of IBD among hospitalized patients admitted to LRH

The study was conducted as a longitudinal study involving all the medical wards in the Lady Ridgeway Hospital. Children (age <5 year) who fulfilled inclusion criteriae were enrolled in the study. Diagnosis given by the consultant Paediatrician at the time of discharge was considered as the final diagnosis.

Inclusion Criteriae

- ▶ **Meningitis**-Any child aged 0-59 months admitted with sudden onset of fever (>38⁰ C) with *one of the following*
 - Neck stiffness
 - Altered consciousness without an alternative diagnosis
 - other meningeal signs
 - Or with clinical diagnosis of meningitis
- ▶ **Pneumonia**-Any child aged 0-59 months admitted with cough or difficulty in breathing when calm
- ▶ **Sepsis**-Any child aged 0-59 months admitted with *at least 2* of the under mentioned without meningitis or pneumonia
 - Inability to drink/breast feed
 - Vomiting
 - Convulsions
 - Prostration/lethargy
 - Severe malnutrition
 - Hypothermia

There were 430 (17.6% of the cases) meningitis cases, 1754 (71.7%) pneumonia cases and 261 (10.7%) sepsis cases.

More than half (62.5%) of the meningitis cases were in the < 2 years old category and pneumonia and sepsis cases for the same age category was 62.3% and 77.4% respectively. All three disease entities (meningitis, pneumonia and sepsis cases) showed a decreasing trend with advancing ages. Most of the blood cultures (meningitis-93.6%, pneumonia-96.3% and sepsis 84.9%) were negative (results of 1910 cultures are available) and *Streptococcus pneumoniae* was positive in 1.1% of meningitis cases and 0.8% of sepsis cases. *Haemophilus influenzae* type b (Hib) was grown in 1.3% of meningitis cases and 0.3% of pneumonia cases. *Neisseria meningitides* was positive in 1.3% of sepsis cases, 0.3% of meningitis cases and 0.2% of pneumonia cases.

Majority of the Cerebro-Spinal Fluid samples (91%) did not show any growth or tested negative when antigen tests were conducted. *Streptococcus pneumoniae* was positive in 1.3% of cases and *Haemophilus influenzae* type b (Hib) was positive in 2.8% of cases.

It is evident that 10-valent pneumococcal vaccine (PCV10) is effective against 71.6% of sero types causing IPD and the other 13-valent pneumococcal vaccine (PCV13) is effective against 75.6% of the serotypes causing IPD in Sri Lanka.

Forum concluded that Sri Lanka does not have sufficient facilities to isolate fastidious organisms like *Streptococcus pneumonia* currently and that further discussion by an expert panel is necessary to decide on the introduction of pneumococcal vaccine to Sri Lanka.

Rota virus Gastro-enteritis Surveillance in Sri Lanka-Dr.Madhava Gunasekara

Rotavirus is the most common cause of severe diarrhoeal disease in infants and young children globally. According to WHO, 36% of hospitalizations for diarrhoea among children aged <5 years were caused by rotavirus infection. Children under five years of age, especially those between 6 months and two years are most vulnerable to the disease.

Unique features of Gastro-enteritis situation in Sri Lanka are

- Low mortality due to diarrhoea
- Significantly high morbidity
- Wide and rational use of ORS
- Low use of anti-diarrhoeal medication

Who funded RVGE surveillance was started in 2009 with the funding of WHO and still continuing. Majority of the samples (>90%) were collected from Lady Ridgeway Hospital. Samples were collected from North Colombo Teaching Hospital-Ragama, TH Peradeniya, TH Matara, TH Jaffna, TH Batticaloa, TH Anuradhapura, DGH Nuwara-Eliya, DGH Badulla also.

This is a joint activity of the Epidemiology Unit, MRI and sentinel surveillance sites

Objective of the surveillance was to generate comprehensive local epidemiological data on diarrhoeal disease due to rota virus in Sri Lanka

Inclusion criteriae

Any child under 5 years of age who is admitted for treatment of acute watery diarrhoea /gastro enteritis (≤14days duration) to a hospital participating in the study.

Exclusion criteria

Children with bloody diarrhoea and children transferred from another hospital

During this period (2009-2014), a total of 1663 children (stool samples) were tested for RVGE

Proportion of children positive for Rota virus infection ranged from 26.6% in 2009 41.4% in 2011 (average 33.4%). Highest positivity rate for rota virus was present in the 1-2 year olds (38.6%) and lowest positivity rate for rota virus was present in the <6 months age group. A significant proportion (34.7%) of children admitted with rota virus gastro-enteritis was in the 1-2 year old age group only 8.6% of the children were in < 6 months age group.

A majority of the Rota virus gastro-enteritis cases were caused by G9 P[8] (62.5%) in 2009, G2P[4] in 2012 (78.4%) and G1P[8] (49.5%) in 2013. Therefore, genotypes causing Rota virus shows a wide variation with time and major proportion of the Rota virus infections are not covered by existing vaccines.

The forum concluded that the existing good diarrhoea management practices resulting in low mortality does not warrant introduction of Rota virus Vaccine in the near future.

Hepatitis B Sero Survey-Dr.Jagath Amarasekara

Preliminary findings of the hepatitis B Sero-survey conducted in Kalutara district, Sri Lanka in 2014 was presented at the Immunization Summit by Dr. Jagath Amarasekera, Consultant Epidemiologist. The survey was conducted to assess the impact of the Hepatitis B immunization programme. A total of 407 children aged between 1 to 5 years took part in this community survey. It was conducted jointly by the Epidemiology Unit and Medical Research Institute (MRI).

All children who took part in the survey had been vaccinated against Hepatitis B infection and none of the children had any acute or chronic Hepatitis B infection. Over 75% of children had a protective level (10mIU/ml or above) of humeral immunity against the infection. Hence the results mentioned above are suggestive of a highly successful Hepatitis B immunization programme in Sri Lanka.