WEEKLY EPIDEMIOLOGICAL REPORT

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Applicability of Dengue Vaccines

The number of dengue cases reported annually to WHO is reaching 2.2 million in 2010 and 3.2 million in 2015 although it is believed that there is substantial under-reporting of dengue within health systems of countries. Based on mathematical modelling, the global annual incidence is estimated to be about 50–100 million symptomatic cases in recent years, predominantly in Asia, followed by Latin America and Africa, with clinical cases likely to represent about 25% of all dengue virus infections.

Immunity and Dengue

Dengue viruses are members of the genus Flavivirus, within the family Flaviviridae. There are 4 dengue virus serotypes (DEN-1, DEN-2, DEN-3 and DEN-4), all of which circulate globally. The 4 serotypes share only about 60-75% identity at the amino acid level, and are therefore considered as distinct viruses. Most endemic countries report circulation of all 4 serotypes in recent years, and it is known as dengue hyperendemicity.

Immune responses stimulated by natural exposure to bites of mosquitoes carrying dengue viruses are only partially understood and is complicated by the interrelatedness of host responses to the 4 distinct dengue serotypes. Dengue virus infection induces a high-titre of neutralizing antibody, which is believed to be an important component of the protective immune response. Following a primary infection with one dengue virus serotype, protection against the infecting serotype (homotypic protection) is considered long-lasting. Temporary cross-protection is induced to the other serotypes (heterotypic protection), lasting for about 2 years on average. It is well accepted that following waning of cross-neutralizing antibodies, severe illness is more likely to occur with a second dengue virus infection than with the first dengue virus infection (relative risk RR of nearly 7, although some other studies have found higher or lower RRs). Following recovery from a second infection, broadly neutralizing antibodies are induced (multitypic protection), so that severe disease with subsequent infections is considered rare. The mechanism causing greater severity of the second dengue virus infection is not well understood although antibody-dependent enhancement, cytokine storm, or cross-reactive T-cells have been implicated in the pathogenesis.

Dengue Vaccines

At present, one dengue vaccine, a live attenuated (recombinant) tetravalent vaccine has been registered in several countries while several other candidates are in clinical development. There are 2 other candidates currently under evaluation in Phase III trials which are also tetravalent live attenuated (recombinant) vaccines.

Based on data collected from Phase II studies, the majority of sero-positive subjects have a tetravalent response after two doses. In sero-negative subjects, the proportion with a tetravalent response is lower than in the sero-positive subjects. The 3-dose series increased the proportion of subjects with a tetravalent response as compared to the 2-dose series, although many sero-negative subjects still did not have a tetravalent response after 3 doses. However, seroconversion alone does not predict protection. Additional investigations are ongoing to further characterize the relationship between immunologic markers and protection against disease.

Vaccine efficacy was higher in individuals who were seropositive at baseline compared to those who were seronegative at baseline. Age and sero-positivity were highly correlated in the trials. Efficacy varied by country to country in the studies, ranging from 31.3% (95% CI 1.3%–51.9%) in Mexico to 79.0% (95% CI 52.3%–91.5%) in Malaysia. This variability in efficacy likely reflects, at least in part, the baseline seropositivity and circulating serotypes, both of which affect the performance of the vaccine.

During the vaccine studies, an increased risk of hospitalized dengue was identified in one age group (2–5 years) which was unlikely to be due to chance. Several hypotheses suggested to explain this, including that in sero-negative children, of whom there is a higher percentage in the youngest age groups, the vaccine may act as a silent natural infection that primes sero-negative vaccinees to experience a secondary-like infection upon their first exposure to dengue virus. Therefore it was decided to start the indicated age range for vaccination at 9 years. Vaccination may be ineffective or may theoretically even increase the future risk of dengue illness in those who are sero-negative at the time of first vaccination regardless of age. If this is the case, even in high transmission settings there may be increased risk among seronegative persons despite a reduction in dengue illness at the population level.

Mathematical models have been developed to predict the impact of dengue vaccines when administered in a routine immunization programme. Comparing several mathematical models of the potential impact, it was assumed that (i) the vaccine mimics a silent natural infection, providing temporary cross-protection against all serotypes and (ii) subsequently modifies (in the long-term) the likelihood of experiencing symptomatic and severe dengue illness. The models also assumed that vaccination is implemented in settings with existing dengue control interventions and treatment. With an assumed vaccine coverage of 80% for the 3-dose series and vaccination at 9 years of age, all models found that it would result in an overall reduction in dengue illness in settings with moderate to high transmission intensity

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(sero-prevalence ≥50% at 9 years). The impact of vaccination was greatest in high transmission intensity settings (sero-prevalence ≥70% at 9 years), where the reduction in symptomatic and hospitalized dengue was predicted to be from 10% to 30% over the next 30-year period. The models also predicted that in very low transmission intensity settings (sero-prevalence 10% at 9 years) vaccination of 9 year-olds was likely to increase dengue hospitalization rates. Some models predicted the same effect when sero-prevalence at 9 years was 30%. This was due to a key assumption used in the models, that vaccination acts like an asymptomatic natural infection and hence primes seronegative recipients to have a secondary-like infection when they are exposed to dengue for the first time. In low transmission settings, where a high proportion of the population never experiences a second dengue virus infection, vaccination could therefore lead to an increase in the incidence of dengue illness.

The cost-effectiveness of vaccines was also assessed in the modelling comparison. As the cost of vaccine procurement and delivery was unknown as yet, the analyses were presented as costs per fully vaccinated person. One DALY averted was valued at around US$ 2000 based on benchmarking the costs against alternative interventional strategies being carried out to prevent dengue. Against this benchmark, in settings with sero-prevalence in the range of 50%–90% at age 9 years, vaccination was predicted to be cost-effective if the total cost of fully vaccinating one person were less than US$ 15–40 in the public health perspective. It should be noted, however, that the modelling comparison results were based on regional indicators and should not be used as a substitute for country-specific analyses to effect local decision-making.

WHO is in the position that each country should consider introduction of the dengue vaccine only in geographic settings (national or subnational) where epidemiological data indicate a high burden of disease. In defining populations to be targeted for vaccination, prior infection with dengue virus of any serotype, as measured by sero-prevalence, should be approximately 70% or greater, in the age group targeted for vaccination, in order to maximize public health impact and cost-effectiveness.

While age-stratified sero-surveys are currently the best method for selecting populations suitable for vaccination, subnational, age-stratified surveillance data may be used to help guide vaccine decision making. Preferably a combination of sero-prevalence, surveillance data, and programmatic factors should define the target population. The target age for routine vaccination should be defined by each country, based on maximizing vaccination impact and programmatic feasibility of targeting specific age groups.

Dengue vaccine introduction should be carried out as a part of a comprehensive dengue control strategy, including well-executed and sustained vector control, evidence-based best practices for clinical care for all patients with dengue illness, and strong dengue surveillance. Vaccine introduction must be accompanied by a targeted communication strategy.

Although the dengue vaccine may be introduced during an outbreak as part of an overall dengue control strategy, vaccination is not expected to have a significant impact on the course of an ongoing outbreak.

Are we ready for the Dengue Vaccine in Sri Lanka?

The above details are mainly adopted from the WHO position paper on Dengue Vaccines published in mid-2016, which encompasses relevant clinical studies on available vaccine candidates. It is clearly evident that the implementation of a vaccine programme against dengue in any country should be carried out on a scientific approach rather than as an ad-hoc or politically driven scheme.

Current disease surveillance system in place in our country is largely based on syndromic diagnosis of suspected cases which is insufficient to assess the national and sub national level of dengue transmission dynamics. The current surveillance system does not capture morbidity data from out-patient departments, laboratories and the community. Therefore, the patients who do not get admitted to hospitals, particularly those with mild symptoms or clinically unapparent infections are unlikely to be reported and are not reflected in the morbidity figures. From the inpatients too, a proportion of cases may be missed from hospitals in different parts of the country. Consequently, under reporting is a significant problem with the routine surveillance mechanism currently in place. Therefore, an assessment to evaluate the vulnerable ages and the serological extent of dengue transmission is very important to recognize the true disease burden. Knowledge of the strength of dengue transmission is important for evidence based effective control and preventive strategies, particularly in the event of future vaccine introduction.

It is important that we have an understanding of the sero-prevalence of dengue in the country, or at least in the high-risk areas like western province or in the Colombo district. In this backdrop, a community based descriptive study of dengue sero-epidemiology in the Colombo district is being carried out by the Epidemiology Unit. Age-specific dengue sero-prevalence in the metropolitan, urban and rural populations in the Colombo district will be assessed in this study. The outcome of this study will be useful for obtaining more accurate estimates of the disease burden, both serologically and economically, as another component of this study will look into assessing the disease burden of dengue, through Disability Adjusted Life Years or DALYs, which incidentally will be the first time it is attempted in Sri Lanka.

Compiled by:

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Table 1 : Water Quality Surveillance
Number of microbiological water samples February 2017

District	MOH areas	No: Expected *	No: Received
Colombo	15	90	81
Gampaha	15	90	NR
Kalutara	12	72	NR
Kalutara NIHS	2	12	NR
Kandy	23	138	NR
Matale	13	78	NR
Nuwara Eliya	13	78	12
Galle	20	120	NR
Matara	17	102	5
Hambantota	12	72	NR
Jaffna	12	72	136
Kilinochchi	4	24	19
Manner	5	30	0
Vavuniya	4	24	NR
Mullatvu	5	30	NR
Batticaloa	14	84	49
Ampara	7	42	NR
Trincomalee	11	66	0
Kurunegala	29	174	NR
Puttalam	13	78	NR
Anuradhapura	19	114	NR
Polonnaruwa	7	42	34
Badulla	16	96	123
Moneragala	11	66	73
Rathnapura	18	108	NR
Kegalle	11	66	14
Kalmunai	13	78	NR

* No of samples expected (6 / MOH area / Month)
NR = Return not received

Table 1: Selected notifiable diseases reported by Medical Officers of Health 11th – 17th March 2017 (11th Week)

RDHS Division	Dengue Fever		Dysentery		Encephalitis		Enteric Fever		Food Poisoning		Leptospirosis		Typhus Fever		Viral Hepatitis		Human Rabies		Chickenpox		Meningitis		Leishmani-asis		WRCD	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	T*	C**
Colombo	469	6076	0	27	0	1	4	11	1	4	3	19	0	1	0	5	0	0	14	83	0	10	0	1	**75**	**94**
Gampaha	381	3674	0	14	0	8	0	9	0	8	0	19	0	5	0	5	0	1	4	61	0	14	0	4	**27**	**67**
Kalutara	209	1526	4	16	0	2	1	2	3	15	2	51	0	2	0	0	0	0	19	147	2	29	0	0	**86**	**93**
Kandy	82	713	1	25	0	3	1	1	0	0	1	12	5	40	1	6	0	1	12	92	0	13	0	2	**91**	**100**
Matale	30	334	0	5	0	0	0	0	0	0	1	13	0	1	0	3	0	0	3	10	1	23	0	2	**54**	**100**
NuwaraEliya	4	107	0	7	0	1	1	3	0	0	1	11	6	42	0	4	0	0	3	37	2	16	0	0	**85**	**100**
Galle	61	1697	2	15	0	4	0	4	1	9	3	47	1	18	0	0	0	0	6	78	0	16	0	0	**75**	**95**
Hambantota	65	697	0	13	0	2	0	5	0	15	1	14	4	21	0	4	0	0	3	70	1	8	1	110	**75**	**100**
Matara	49	1002	0	15	0	4	0	0	0	2	4	21	0	9	0	2	0	1	6	54	0	2	1	32	**94**	**94**
Jaffna	154	1585	1	80	1	4	0	13	0	24	0	17	14	290	1	4	0	0	3	89	2	16	0	0	**100**	**100**
Kilinochchi	8	162	0	6	0	0	0	3	0	0	0	2	0	9	0	2	0	0	0	0	0	0	0	3	**25**	**50**
Mannar	9	279	0	4	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	4	0	0	0	0	**100**	**100**
Vavuniya	34	217	1	7	0	0	0	10	0	2	1	11	0	2	0	1	0	0	0	14	0	0	2	6	**75**	**100**
Mullaitivu	5	81	0	2	0	0	0	3	0	0	0	7	1	3	0	0	0	0	0	1	0	5	0	1	**100**	**100**
Batticaloa	152	1103	0	37	0	8	0	9	0	1	0	6	0	0	0	2	0	0	0	53	0	12	0	1	**43**	**93**
Ampara	13	137	1	7	1	1	0	1	0	0	0	5	0	1	0	1	0	0	1	45	1	6	0	1	**71**	**100**
Trincomalee	396	2302	0	3	0	1	0	3	0	1	2	6	0	5	0	7	0	0	1	46	1	5	0	1	**62**	**77**
Kurunegala	89	1073	0	22	0	0	0	0	0	2	1	29	0	17	0	5	0	0	16	168	1	15	4	37	**69**	**93**
Puttalam	45	446	0	17	0	1	0	1	0	0	0	4	0	10	0	1	0	0	8	63	0	13	0	1	**57**	**64**
Anuradhapura	49	448	0	12	0	1	0	0	0	2	0	23	0	9	0	6	0	0	1	94	0	17	0	78	**47**	**89**
Polonnaruwa	62	1067	0	7	1	4	0	4	0	0	1	13	1	3	0	1	0	0	5	68	0	6	3	41	**86**	**86**
Badulla	14	161	3	29	0	3	2	4	0	1	1	15	0	11	1	11	0	1	5	78	2	49	1	5	**82**	**94**
Monaragala	17	431	1	13	0	2	0	0	0	2	3	24	5	43	2	9	0	0	0	29	2	18	0	4	**73**	**100**
Ratnapura	14	241	4	54	0	35	0	4	0	3	4	94	1	13	3	21	0	0	7	99	3	60	0	0	**61**	**94**
Kegalle	91	1091	1	15	0	4	0	1	0	13	1	16	6	24	1	4	0	0	9	69	1	25	2	4	**73**	**91**
Kalmune	81	672	0	18	0	4	0	1	0	4	0	3	0	0	0	0	0	0	0	73	0	4	0	0	**46**	**69**
SRILANKA	**2594**	**27322**	**18**	**470**	**3**	**93**	**9**	**93**	**5**	**108**	**30**	**482**	**44**	**580**	**9**	**104**	**0**	**4**	**126**	**1625**	**19**	**382**	**14**	**334**	**70**	**91**

Source: Weekly Returns of Communicable Diseases (WRCD).

*T=Timeliness refers to returns received on or before 17th March , 2017 Total number of reporting units 337 Number of reporting units data provided for the current week: 316 C**-Completeness

A = Cases reported during the current week. **B** = Cumulative cases for the year.

Table 2: Vaccine-Preventable Diseases & AFP

11th – 17th March 2017 (11th Week)

Disease	No. of Cases by Province									Number of cases during current week in 2017	Number of cases during same week in 2016	Total number of cases to date in 2017	Total number of cases to date in 2016	Difference between the number of cases to date in 2017 & 2016
	W	C	S	N	E	NW	NC	U	Sab					
AFP*	02	00	00	00	00	00	00	00	00	02	00	24	13	+84.6%
Diphtheria	00	00	00	00	00	00	00	00	00	00	00	00	00	0%
Mumps	01	00	02	00	00	00	01	00	00	04	02	65	92	- 29.3%
Measles	01	01	00	00	01	00	00	00	00	03	08	79	162	-51.2%
Rubella	00	00	00	00	00	00	00	00	00	00	00	05	05	0%
CRS**	00	00	00	00	00	00	00	00	00	00	00	00	00	0%
Tetanus	00	00	00	00	00	00	00	00	00	00	00	05	02	60%
Neonatal Tetanus	00	00	00	00	00	00	00	00	00	00	00	00	00	0%
Japanese Encephalitis	00	00	00	00	00	00	00	00	00	01	00	21	00	0%
Whooping Cough	00	00	00	00	00	00	00	00	00	00	02	04	21	-80.9%
Tuberculosis	102	19	05	06	08	15	14	03	10	182	244	1723	1896	- 9.1%

Key to Table 1 & 2

Provinces: **W**: Western, **C**: Central, **S**: Southern, **N**: North, **E**: East, **NC**: North Central, **NW**: North Western, **U**: Uva, **Sab**: Sabaragamuwa.

RDHS Divisions: **CB**: Colombo, **GM**: Gampaha, **KL**: Kalutara, **KD**: Kandy, **ML**: Matale, **NE**: Nuwara Eliya, **GL**: Galle, **HB**: Hambantota, **MT**: Matara, **JF**: Jaffna, **KN**: Killinochchi, **MN**: Mannar, **VA**: Vavuniya, **MU**: Mullaitivu, **BT**: Batticaloa, **AM**: Ampara, **TR**: Trincomalee, **KM**: Kalmunai, **KR**: Kurunegala, **PU**: Puttalam, **AP**: Anuradhapura, **PO**: Polonnaruwa, **BD**: Badulla, **MO**: Moneragala, **RP**: Ratnapura, **KG**: Kegalle.

Data Sources:

Weekly Return of Communicable Diseases: Diphtheria, Measles, Tetanus, Neonatal Tetanus, Whooping Cough, Chickenpox, Meningitis, Mumps., Rubella, CRS,

Special Surveillance: AFP* (Acute Flaccid Paralysis), Japanese Encephalitis

CRS =**Congenital Rubella Syndrome

AFP and all clinically confirmed Vaccine Preventable Diseases except Tuberculosis and Mumps should be investigated by the MOH

Influenza Surveillance in Sentinel Hospitals - ILI & SARI								
Month	Human					Animal		
	No Received	ILI	SARI	Infl A	Infl B	Pooled samples	Serum Samples	Positives
February	7801	27	114	29	0	1697	395	0

Source: Medical Research Institute & Veterinary Research Institute

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Comments and contributions for publication in the WER Sri Lanka are welcome. However, the editor reserves the right to accept or reject items for publication. All correspondence should be mailed to The Editor, WER Sri Lanka, Epidemiological Unit, P.O. Box 1567, Colombo or sent by E-mail to **chepid@sltnet.lk. Prior approval should be obtained from the Epidemiology Unit before publishing data in this publication**

ON STATE SERVICE

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