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Immunobridging Trials to Evaluate Vaccines

***This is the first article of two in a series on* "Immunobridging Trials to Evaluate Vacines"**

Infectious diseases continue to cause significant illness and death worldwide, despite the availability of advanced medical tools like vaccines, treatments, and antibodies. One challenge is that infectious pathogens constantly mutate to escape human immunity, making these tools less effective over time. To keep up with evolving pathogens, faster ways to assess and approve new medical solutions are essential. These pathways help protect people from infections and improve their quality of life.

Immunobridging is a strategy that speeds up access to effective tools for tackling evolving pathogens. It uses surrogate immune response measures, like antibody levels, to predict how well a new vaccine or drug will work. *'Surrogate immunological measures' are indirect markers or indicators used to predict the effectiveness of a vaccine, drug etc., based on immune responses, rather than relying on clinical outcomes (e.g. prevention of disease or death).* These measures serve as substitutes for direct evidence of clinical benefit. Examples in practice include COVID-19 HPV & Influenza vaccines. Although immunobridging has been used for years, such as with influenza vaccines, many healthcare providers are still unfamiliar with it. Greater awareness of this approach is especially important now, as the risk of epidemics and pandemics continues to grow.

Normally, vaccines must pass rigorous phase 3 trials with placebo controls before they can be approved. However, this can be challenging when there are too few cases of disease or volunteers for traditional trials. In addition, when new variants emerge, evidence from older phase 3 trials may no longer be relevant. In such situations, **phase 3b immunobridging trials** provide a faster, safer, and more efficient way to evaluate updated vaccines or treatments.

What is Immunobridging?

Immunobridging is a trial methodology that infers the effectiveness of a new drug or vaccine through a surrogate immunological measure of efficacy. It compares the immune response from the new treatment to results from earlier studies of similar treatments.

Immunobridging trials are appropriate for interventions that rely on pathogen-mediated humoral immunity (antibody-based immunity) or passive prophylaxis with antibodies, as these outcomes can be evaluated using laboratory assays.

In vaccine trials, Immunobridging is an alternative to traditional vaccine effectiveness trials. It compares the immune response of a new vaccine to that of an already approved vaccine, showing that both produce similar immune responses.

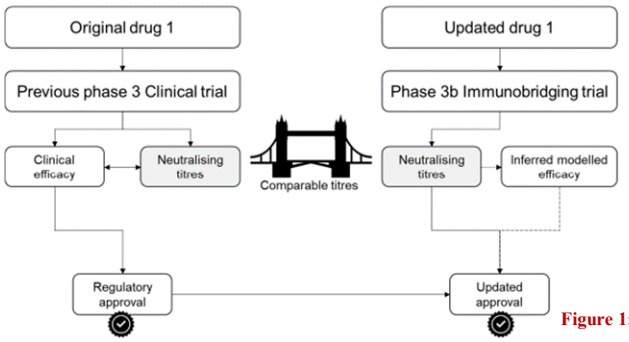

Figure 1: Immunobridging Paradigm

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Purpose of Immunobridging

Immunobridging helps avoid the need for large-scale vaccine effectiveness trials when expanding a vaccine's use to new groups or conditions. When immune responses match those linked to vaccine-induced immunity, immunogenicity data can be used to predict effectiveness. The WHO describes **Immunobridging** as *a regulatory and scientific approach to infer vaccine effectiveness through comparison of immune response markers elicited by a vaccine under different sets of conditions.* In simple terms, it evaluates immune response markers from a vaccine in varying situations to estimate its efficacy.

It is used to assess vaccine effectiveness in new scenarios after it has been proven effective in clinical trials under different conditions. These scenarios include:

- Use in different age or demographic groups.
- Different dose levels or schedules.
- Modified vaccine formulations, such as adding or changing antigens.
- Simultaneous administration with other vaccines (to check for immune interference).
- Use of a different vaccine platform (in specific cases).

Immunobridging provides a scientifically justified way to avoid repeating clinical endpoint efficacy studies when enough evidence supports the new application.

Schematic of Immunobridging

In immunobridging, study subjects are divided into two groups:

1. **Reference Group**:
   - Includes participants from earlier clinical trials where the vaccine or treatment was proven effective.
   - The formulation, dose, and schedule used in these trials are recorded.
2. **Test Group**:
   - Includes new participants volunteering for trials.
   - The formulation, dose, and schedule for this group are finalized based on statistical hypotheses.

The test group is designed to match the reference group as closely as possible, with only a few controlled differences. The hypothesis leads to the selection of immune markers.

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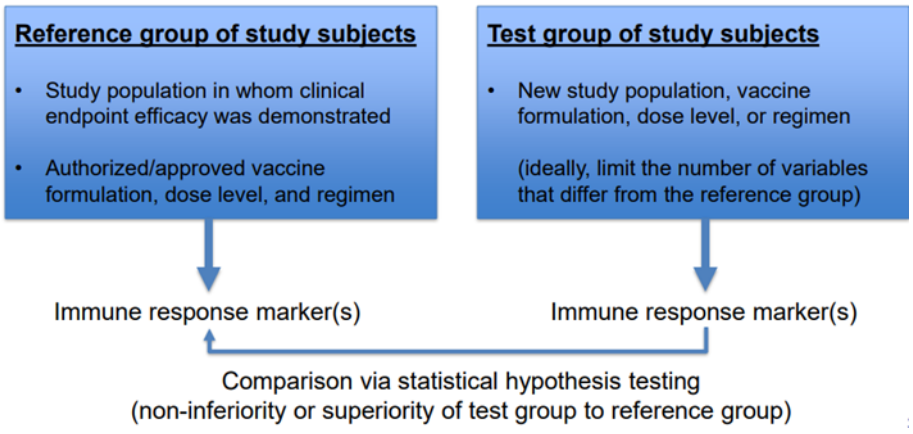

Figure 2: Schematic of Immunobridging

To be continued….

Table 1: Selected notifiable diseases reported by Medical Officers of Health 23rd–29th Nov 2024 (48th Week)

RDHS	Dengue Fever		Dysentery		Encephalitis		En. Fever		F. Poisoning		Leptospirosis		Typhus F.		Viral Hep.		H. Rabiies		Chickenpox		Meningitis		Leishmania-		Tuberculosis		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	A	B	T*	C**
Colombo	185	10718	0	44	0	11	0	49	0	25	27	563	1	9	0	9	0	0	14	569	3	49	0	2	52	2031	100	100
Gampaha	186	5332	2	45	0	39	0	14	3	80	51	924	0	12	1	13	0	0	21	487	7	139	0	28	14	1105	80	100
Kalutara	34	2599	1	35	0	3	0	38	0	38	26	870	0	8	0	11	0	1	16	654	0	61	0	2	14	556	87	100
Kandy	63	4304	3	41	0	7	0	10	0	72	7	262	0	38	0	13	0	3	5	392	0	15	5	64	0	554	100	100
Matale	31	915	0	18	1	4	0	8	0	30	8	111	0	6	0	9	0	0	6	149	0	24	14	364	3	122	100	100
Nuwara Eliya	3	337	6	143	1	8	0	11	0	209	2	170	2	48	1	10	0	0	10	274	1	19	0	1	0	254	85	100
Galle	26	2023	3	59	0	22	0	12	3	112	40	964	2	121	0	11	0	2	31	846	2	100	0	5	10	428	100	100
Hambantota	6	814	0	28	0	4	0	6	0	50	17	514	0	48	1	9	0	2	2	304	2	32	5	480	5	147	100	100
Matara	20	1121	1	14	0	6	1	3	0	38	38	627	0	29	0	24	0	0	13	370	1	77	2	116	1	162	100	100
Jaffna	47	5454	1	70	0	2	1	28	0	48	4	30	25	524	0	7	0	1	5	218	0	33	0	1	0	238	93	93
Kilinochchi	1	304	0	17	0	0	0	2	0	2	0	20	0	11	0	0	0	2	0	15	0	6	0	2	0	27	100	100
Mannar	6	319	0	18	0	0	0	1	1	7	1	31	0	13	0	1	0	0	0	12	0	14	1	3	1	57	100	100
Vavuniya	3	182	0	13	0	1	0	2	0	22	1	110	0	5	0	4	0	0	3	46	0	26	0	12	0	40	100	100
Mullaitivu	3	217	0	10	0	0	0	0	0	22	2	74	0	11	0	0	0	2	0	11	1	6	2	16	0	33	100	100
Batticaloa	21	1531	3	128	0	17	0	7	1	65	7	85	0	3	0	24	0	2	5	160	0	51	0	4	3	149	93	100
Ampara	4	259	0	39	0	4	0	0	0	23	16	223	0	2	1	7	0	1	5	134	2	39	2	26	1	107	86	100
Trincomalee	9	699	1	22	0	1	0	3	2	13	6	152	3	15	0	4	0	0	2	107	0	23	1	19	0	114	100	100
Kurunegala	20	2142	1	56	0	37	0	3	1	356	47	978	1	40	1	10	0	4	21	612	3	273	10	619	11	456	97	100
Puttalam	23	1152	1	14	0	4	0	4	0	4	14	284	0	38	0	4	0	1	7	136	4	85	0	36	0	216	92	100
Anuradhapura	12	740	2	36	0	8	0	3	4	47	13	431	1	33	1	16	0	1	12	296	3	68	11	854	6	273	96	100
Polonnaruwa	17	398	0	27	0	3	0	1	1	33	26	285	1	3	2	61	0	1	4	159	0	32	7	492	0	110	100	100
Badulla	15	831	2	41	0	11	0	9	0	58	4	475	0	53	2	51	0	0	13	394	1	41	1	45	3	232	88	100
Monaragala	20	968	1	22	0	5	0	3	0	88	16	662	0	35	2	69	0	1	4	176	2	100	3	246	3	125	91	100
Ratnapura	53	2766	7	127	1	12	0	9	0	34	83	2029	1	35	0	31	1	3	2	364	5	140	3	173	11	366	90	100
Kegalle	23	1907	0	31	0	15	0	10	1	16	36	876	0	33	1	15	0	1	23	904	5	85	1	31	4	339	82	100
Kalmunai	1	702	0	18	0	1	0	2	0	30	3	75	0	5	0	4	0	0	3	232	4	31	0	0	3	136	100	100
SRILANKA	832	48734	**35**	**1116**	**3**	**225**	**2**	**238**	**17**	**1522**	**495**	**11825**	**37**	**1178**	**13**	**417**	**1**	**28**	**227**	**8021**	**46**	**1569**	**68**	**3641**	**145**	**8311**	**95**	**99**

Source: Weekly Returns of Communicable Diseases (esurvillance.epid.gov.lk). T=Timeliness refers to returns received on or before 29th Nov, 2024 Total number of reporting units 358 Number of reporting units data provided for the current week: 358**C****-Completeness *

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

Table 2: Vaccine-Preventable Diseases & AFP

23rd – 29th Nov 2024 (48th Week)

Disease	No. of Cases by Province									Number of cases during current week in 2024	Number of cases during same week in 2023	Total number of cases to date in 2024	Total number of cases to date in 2023	Difference between the number of cases to date in 2024 & 2023
	W	C	S	N	E	NW	NC	U	Sab					
AFP*	00	00	00	00	00	00	00	00	00	00	02	72	89	-19.1%
Diphtheria	00	00	00	00	00	00	00	00	00	00	00	00	00	0 %
Mumps	01	00	01	06	00	00	01	03	00	12	07	275	212	29.7 %
Measles	00	00	00	00	00	00	00	00	01	01	13	296	757	-60.8 %
Rubella	00	00	00	00	00	00	00	00	00	00	00	02	09	-77.7%
CRS**	00	00	00	00	00	00	00	00	00	00	00	00	02	-100 %
Tetanus	00	00	00	00	00	00	00	00	00	00	00	05	06	-16.6 %
Neonatal Tetanus	00	00	00	00	00	00	00	00	00	00	00	00	00	0 %
Japanese Enceph-alitis	00	00	00	00	00	00	00	00	00	00	02	11	04	175 %
Whooping Cough	01	01	01	00	00	00	02	00	00	05	00	66	07	842.8 %

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

NA = Not Available

Take prophylaxis medications for leptospirosis during the paddy cultivation and harvesting seasons.

It is provided free by the MOH office / Public Health Inspectors.

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**

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