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Immunobridging Trials to Evaluate Vaccines - Part II

This is the second article of two in a series on "Immunobridging Trials to Evaluate Vaccines"

Selection of Immune Markers for Immunobridging

Immune markers, often antibody responses measured with a validated test, are key in immunobridging. If an immune marker is scientifically proven to predict protection, immunobridging can assess measures like sero-response or sero-protection rates. For instance, the effectiveness of new Hepatitis B vaccines can be inferred using an anti-HBsAg level above 10 mIU/mL as a protective marker. A normal antibody response to predict protection raises the possibility that Immunobridging may be acceptable.

Immunobridging may also be acceptable with immune markers that are clinically relevant but not fully established to predict protection. This depends on:

- **Evidence Strength**:

The evidence supporting the marker's clinical relevance and any measures to reduce risks of uncertainty or error.

- **Multiple Endpoints**:

Using more than one measure of the same marker to compare responses, such as geometric mean titer for higher levels and zero-response rate for lower levels.

Key Considerations for Immunobridging Success Criteria

- The criteria should be strict enough to avoid wrongly concluding that a vaccine is effective.
- Common regulatory standards use:
  - A **1.5-fold non-inferiority margin** for geometric mean titer ratios.
  - A **10% non-inferiority margin** for differences in sero-response or sero-protection rates.
- In some cases, more or less stringent criteria may be appropriate.
- **Serial Immunobridging** (repeated bridging with new standards) should be avoided, even with strict criteria, to prevent **'biocreep'** – *a gradual acceptance of a less effective or lower-quality standard, usually in non-inferiority trials, where a new treatment is compared to the existing one to demonstrate that it is not significantly worse.*

Applications & Benefits of Immunobridging Trials

Immunobridging trials play a key role in vaccine development, with examples like pneumococcal and annual influenza vaccines. Influenza vaccines are updated yearly based on antibody titer data linked to clinical protection, avoiding the need for large, time-consuming phase 3 trials. Similarly, HPV vaccines have used immunobridging to cover more strains, optimize doses, and simplify schedules. During COVID-19, immunobridging trials were used to assess new vaccines and re-evaluate existing ones. Advantages of immunobridging trials include:

- Requirement of fewer participants,
- Shorter trial durations speed up regulatory review and approval,
- Timely relevance to evolving pathogens, Reduced costs and simplified trial requirements.

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Parameter	Phase 3 randomised controlled trials	Phase 3b immunobridging trials
Pathogens	Against historical pathogens	Against current pathogens or novel variants or historical pathogens
Trial size	1000–10,000	100–1000
Outcome	Clinical outcomes dependent on pathogen virulence and healthcare system capability, with long follow-up (e.g., hospitalisation and intensive care admission)	Immunological profiles and outcomes dependent on patient's immune system, such as vaccines, or on the pharmacokinetics of the administered products such as monoclonal antibodies (e.g., neutralising antibody titres)
Comparator	Usually, placebo	Previous versions of the product
Patients	Historical participants who may not have had previous infection, vaccines, or boosters	Patients who are representative of the current situation
Investment cost	Sizeable	Modest

Figure 3: Comparison of Phase 3 RCT and Phase 3b immunobridging trials

Conceptual framework

To begin, a traditional phase 3 randomized controlled trial with a positive outcome is required for an investigational product (like a vaccine). This trial should include immunological measures, such as **neutralizing antibody titers,** which were used in COVID-19 studies. *These are an individual patient-level measure of the effectiveness of their antibodies binding to and thus neutralizing a pathogen in vitro. Increasing evidence has shown that neutralizing antibodies area is a valid correlate of protection for COVID-19.* Using neutralizing antibody titers helps correlate the immune response with clinical outcomes from the original trial in a clear, quantitative way. For example, if people who avoided infection had an antibody titer of 100 IU/mL, that could be a surrogate marker for protection. If this marker is strongly linked to clinical benefit, it can serve as a benchmark for future studies of updated vaccines, like in SARS-CoV-2, through phase 3b immunobridging trials.

Limitations

While phase 3b immunobridging trials can be useful for quickly responding to rapidly evolving pathogens, it's important to recognize potential limitations.

- **Reliance on global systems:** Immunobridging depends on global systems to track pathogen evolution, requiring strong diagnostic infrastructure to identify variants.
- **Variability on neutralizing antibody titers**: It relies on reference neutralizing antibody titers from previous trials, which can vary. These titers can differ between variants, change over time, and vary based on clinical outcomes like infection rates or hospitalizations.
- **Lack of robust correlates**: Not all pathogens have clear correlates of protection.
- **Assay consistency: assays used** in the original trial for neutralizing antibody titers must be similar to those used in the secondary trial. Although non-inferiority criteria are well-established (with the lower bound of the confidence interval above the non-inferiority threshold of -10%), there is no consistent standardized method for measuring neutralizing antibody titers in vitro. Variability in assays can affect results, and current tests may not distinguish between vaccine-induced or naturally acquired antibodies.
- **Limited Confidence**: Confidence in immunobridging findings is highest when updates to the product are minor and biologically well-defined. For example, small updates to vaccine epitopes with no changes to the vector are ideal for immunobridging trials.
- **Side Effects**: Immunobridging trials may not accurately predict *the side effects of a new drug. Any new drug under consideration must account for potential toxicities in these trials.

Conclusions

Immunobridging trials offer a promising and efficient way to provide faster protection against infectious diseases, including those that may cause future outbreaks or pandemics, as well as ongoing community infections like RSV and influenza. Phase 3b immunobridging trials have a proven track record in vaccine development.

The main challenge lies in the reliance on surrogate immune markers, which affects confidence in the results. This highlights the need for greater awareness and expertise in this area. Immunobridging has been crucial in ensuring patient safety and improving well-being, particularly for influenza and COVID-19. It also helps maintain continuous access to advanced therapies for patients.

While immunobridging trials could become a standard method for addressing evolving pathogens and ensuring timely updates to treatments, it is important to be mindful of the limitations. Ensuring robust evidence and appropriate application of this approach will be key to its successful use in future vaccine or therapy development.

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Table 1: Selected notifiable diseases reported by Medical Officers of Health 30th–06th Dec 2024 (49th 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	163	10881	0	44	0	11	0	49	0	25	28	591	1	10	0	9	0	0	12	581	9	58	0	2	40	2071	100	100
Gampaha	133	5465	1	46	0	39	0	14	2	82	20	944	0	12	0	13	0	0	13	500	3	142	1	29	18	1123	100	100
Kalutara	28	2627	2	37	0	3	0	38	2	40	56	926	0	8	0	11	0	1	9	663	3	64	0	2	18	574	100	93
Kandy	71	4375	2	43	0	7	0	10	2	74	9	271	0	38	1	14	0	3	13	405	0	15	1	65	2	556	100	100
Matale	37	952	1	19	0	4	0	8	1	31	12	123	0	6	1	10	0	0	0	149	0	24	4	368	2	124	100	100
Nuwara Eliya	2	339	14	157	0	8	0	11	15	224	2	172	3	51	0	10	0	0	9	283	0	19	0	1	12	266	100	100
Galle	37	2060	5	64	0	22	0	12	0	112	25	989	5	126	0	11	0	2	21	867	3	103	0	5	6	434	100	100
Hambantota	15	829	1	29	0	4	1	7	0	50	13	527	0	48	2	11	0	2	8	312	0	32	7	487	3	150	100	100
Matara	15	1136	1	15	1	7	1	4	0	38	30	657	1	30	1	25	0	0	6	376	1	78	3	119	0	162	100	100
Jaffna	35	5489	3	73	0	2	2	30	0	48	2	32	32	556	0	7	0	1	4	222	0	33	0	1	5	243	93	100
Kilinochchi	1	305	0	17	0	0	0	2	0	2	7	27	2	13	0	0	0	2	0	15	0	6	1	3	3	30	100	100
Mannar	2	321	0	18	0	0	0	1	0	7	4	35	0	13	0	1	0	0	0	12	0	14	1	4	0	57	100	100
Vavuniya	2	184	0	13	0	1	0	2	0	22	5	115	1	6	0	4	0	0	1	47	0	26	0	12	5	45	100	100
Mullaitivu	0	217	1	11	0	0	0	0	0	22	1	75	0	11	0	0	0	2	1	12	1	7	1	17	0	33	100	100
Batticaloa	31	1562	2	130	2	19	0	7	0	65	8	93	0	3	0	24	0	2	14	174	2	53	0	4	2	151	100	100
Ampara	2	261	0	39	0	4	0	0	0	23	1	224	0	2	0	7	0	1	1	135	1	40	1	27	1	108	100	100
Trincomalee	14	713	0	22	0	1	0	3	0	13	3	155	0	15	0	4	0	0	4	111	0	23	0	19	8	122	100	100
Kurunegala	17	2159	1	57	3	40	0	3	17	373	50	1028	0	40	1	11	0	4	13	625	3	276	19	638	0	456	100	93
Puttalam	28	1180	1	15	0	4	0	4	0	4	8	292	2	40	1	5	0	1	4	140	0	85	0	36	20	236	100	100
Anuradhapura	7	747	1	37	0	8	0	3	2	49	8	440	0	33	1	17	0	1	9	305	2	70	11	864	3	276	100	86
Polonnaruwa	6	404	1	28	0	3	0	1	0	33	12	297	0	3	3	64	0	1	0	159	2	34	1	493	1	111	100	100
Badulla	15	846	0	41	0	11	0	9	0	58	2	477	1	54	3	54	0	0	4	398	0	41	0	45	5	237	100	100
Monaragala	13	981	0	22	0	5	0	3	5	93	28	690	1	36	3	72	0	1	9	185	1	101	4	250	4	129	100	91
Ratnapura	38	2804	4	131	1	13	0	9	1	35	44	2073	0	35	1	32	1	4	10	374	2	142	7	180	1	367	100	100
Kegalle	21	1928	1	32	2	17	1	11	0	16	32	908	0	33	0	15	0	1	18	922	4	89	0	31	8	347	100	91
Kalmunai	3	705	2	20	0	1	0	2	0	30	4	79	0	5	0	4	0	0	8	240	2	33	0	0	0	136	100	100
SRILANKA	**736**	**49470**	**44**	**1160**	**9**	**234**	**5**	**243**	**47**	**1569**	**414**	**12240**	**49**	**1227**	**18**	**435**	**1**	**29**	**191**	**8212**	**39**	**1608**	**62**	**3702**	**167**	**8478**	**99**	**98**

Source: Weekly Returns of Communicable Diseases (esurvillance.epid.gov.lk). T=Timeliness refers to returns received on or before 06th Dec, 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

30th – 06th Dec 2024 (49th 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	01	00	01	01	00	01	00	04	02	76	92	-17.3%
Diphtheria	00	00	00	00	00	00	00	00	00	00	00	00	00	0 %
Mumps	01	01	00	00	01	01	00	00	03	07	01	282	220	28.1 %
Measles	00	00	00	00	00	00	00	00	00	00	10	296	767	-61.4 %
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	00	14	06	133.3 %
Whooping Cough	02	00	00	00	01	00	02	00	00	03	00	69	07	885.7 %

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.

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