WEEKLY EPIDEMIOLOGICAL REPORT

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Ministry of Health

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Vaccine Clinical Trials- Phase 1, 11, 111

Effective vaccination against certain infectious diseases has helped to protect human lives and improve the quality of life of many. Vaccine development usually takes 10-15 years of laboratory research. During the typical vaccine development timeline each clinical trial phase follows completion of the prior phase. However, during a Public Health Emergency of International Concern (PHEIC), the process of vaccine development is accelerated. During these instances, some clinical trial phases are combined. E.g., SARS-CoV-2 is a coronavirus that shared similarities with SARS-CoV-1 and MERS-CoV, hence prior work on SARS-1and MERS vaccines reduced the time spent on pre-clinical assessment of COVID-19 and the target antigen was identified quickly.

Although, during typical vaccine development manufacturing capacity is scaled up after phase 3 trial and regulatory approval, during accelerated timeline in a pandemic, manufacturing capacity is scaled up during the clinical trial, but at financial risk.

Pre-clinical Trials

Vaccines must go through several clinical trials before they can be licensed to be used in humans. Before a vaccine is tested on people, researchers study its ability to produce an immune response in small animals, such as rats, mice, hamsters, etc. in a laboratory setting. During this phase, researchers may make adjustments to the vaccine to ensure its safety levels and to make it more effective. The effectiveness of a vaccine is the extent to which the vaccine protects people against infection, symptomatic illness, hospitalization, and death.

If the vaccine shows promising results at this stage, it moves forward to the next stage or clinical trials for testing in humans.

Phase 1 Clinical Trials

For phase 1 clinical trials, typically dozens of participants (20-100) are recruited. In this phase, the vaccine dosage and the safety levels are looked into. This includes learning about side effects and studying how well the vaccine works to cause an immune reaction. Phase 1a will trial the vaccine on healthy adults while type 1b will test the vaccine in a more 'relevant' target group. However, different strategies are used when dealing with high-risk target groups. E.g., Infant vaccines are tested on older children before descending to infancy.

During PHEIC, phase 1 trials are completed within two to three months, allowing for two doses of a vaccine two to three weeks apart.

Phase 2 Clinical trials

In phase 2 clinical trials hundreds of participants (100-300) are recruited. These participants should have characteristics (such as age and physical health) similar to the intended recipients of the vaccine. These participants can preferably be recruited from diverse backgrounds to ensure fair representation across different populations.

The trial is designed to generate additional information on the safety of the vaccine and more information on how the vaccine work to cause an immune response (immunogenicity) of the vaccine against the artificial infection and the disease. The percentage reduction of infection and disease in the vaccinated group compared to the un-vaccinated group will be compared.
There are many ways that a researcher can conduct this phase of the trial, but the plan normally involves assigning the participants to different treatment groups. Normally, there is a control group which receives either the current standard care or a 'placebo' pill, which is a sugar pill or harmless injection that doesn't contain the treatment.

This phase will also be used to test the harmonized delivery of the vaccine with the existing immunization schedule. Furthermore, the compatibility of the vaccine with concomitant vaccines (e.g., EPI vaccines) will be ensured during this phase.

Nevertheless, harmonization with the existing immunization schedule is not required when the

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vaccine is developed for a public health emergency of international concern (PHEIC). Further, during these instances, it is important to test for the practicality of conducting mass vaccination campaigns e.g.: modest cold chain requirements, spacing between doses, and multi-dose vials. During these instances phase 2 trials are completed in three to four months, allowing for longer follow-ups to better assess safety and immunogenicity. This timeline is further shortened when phases 1 and 2 are combined. E.g., In many Covid-19 vaccine clinical trials, phase 1 and phase 2 trials were combined to speed up the process.

Phase 2b trials - Volunteer Challenge Studies

In volunteer challenge studies, a group of volunteers are vaccinated with the vaccine following which, the respective virus is being inoculated into the vaccinated person's body. This can be used as an early measure of the efficacy of the candidate vaccines. Such trials may subtract many months from the licensing process, making the vaccines available to the public more quickly.

Human challenge studies have been useful during the introduction of the cholera vaccine, Typhoid vaccine, Shigella vaccine and influenza vaccines.

Phase 3 Clinical Trials

This phase of the trial involves a much larger group of volunteers (300-3000) and primarily focuses on determining whether the vaccine would be safe and effective for a wide variety of people. These studies are often done in several places across the country at the same time. In phase 3 trials too, there is a control group who receives the standard treatment or a placebo. These studies tend to last longer than phase 1 or 2 studies. After the completion of phase 3 trials, the treatment group will be compared with the control group to determine the effectiveness and safety of the vaccine. Assessing short and long-term goals are also a major goal of phase 3 clinical trials.

Regulatory Approval Process

In situations where adequate scientific evidence can be generated to believe that the vaccine is safe and effective to prevent disease, the FDA will authorize its use through an Emergency Use Authorization (EAU) even if the definitive proof of the efficacy of the vaccine is not known, especially for diseases that cause high mortality.

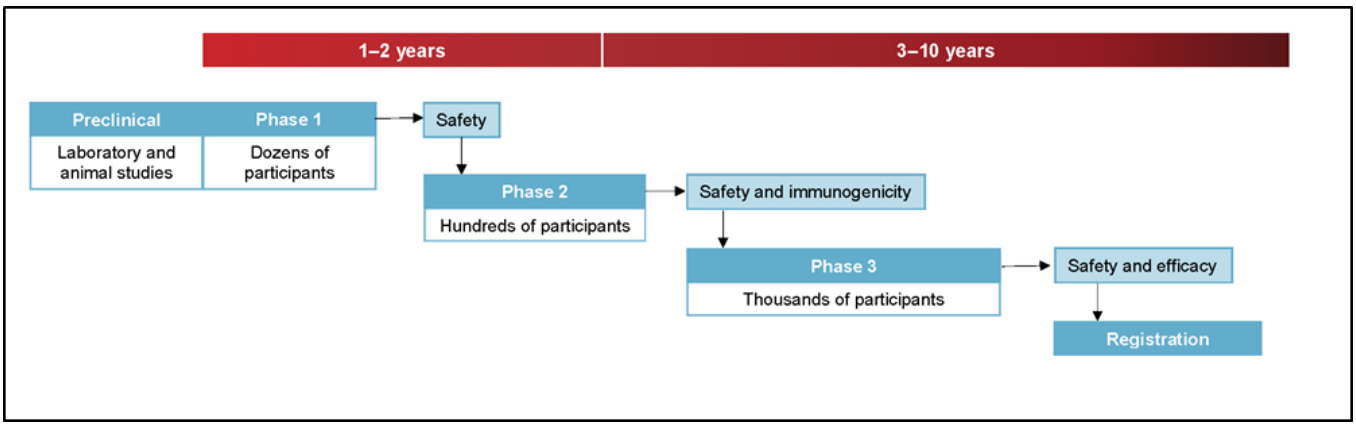

Figure 1: Conventional pathway of vaccine development

(NCIRS- https://ncirs.org.au/phases-clinical-trials)

Reference

https://www.cdc.gov/vaccines/basics/test-approve.html
https://www.vaccinedevelopment.org.uk/ct-overview.html
https://ncirs.org.au/phases-clinical trials#:~:text=It%20takes%20at%20least%201,of%20the%20vaccine%20are%20tested.

Human challenge trials for vaccine development: regulatory considerations, Annex 10, TRS No 1004
https://coronavirus.jhu.edu/vaccines/timeline

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Table 1: Selected notifiable diseases reported by Medical Officers of Health 15th–21st July 2023 (29th Week)

RDHS	Dengue Fever		Dysentery		Encephalit		Enteric Fever		Food Poi-		Leptospirosis		Typhus		Viral		Human		Chickenpox		Meningitis		Leishmania-		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	335	10026	1	8	0	10	0	1	0	7	9	204	0	0	0	3	0	0	8	180	1	28	0	5	**29**	**100**
Gampaha	238	10346	3	15	0	13	0	3	0	3	12	353	0	7	0	11	0	0	5	175	5	52	0	29	**3**	**100**
Kalutara	84	3396	0	14	0	2	0	0	0	6	10	535	0	1	0	5	0	1	11	294	6	64	0	1	**24**	**100**
Kandy	233	4171	0	27	0	0	0	7	0	15	15	183	0	41	0	3	0	1	5	167	0	18	0	22	**87**	**100**
Matale	58	994	0	2	2	2	0	1	2	10	2	115	0	12	0	3	0	0	1	33	0	4	8	201	**24**	**100**
NuwaraEliya	7	164	4	90	0	3	0	3	1	41	3	79	0	49	0	4	0	0	3	87	0	8	0	1	**61**	**100**
Galle	83	1664	0	34	0	12	0	5	0	21	23	594	3	33	0	1	0	1	5	219	1	15	0	2	**37**	**100**
Hambantota	28	1109	0	7	0	3	0	1	0	8	9	216	1	54	0	8	0	0	4	100	0	16	13	396	**26**	**100**
Matara	74	1257	0	19	2	8	0	1	0	12	2	384	3	23	0	3	0	2	3	175	1	16	4	115	**54**	**100**
Jaffna	27	1728	1	55	0	2	0	9	0	17	1	9	5	483	0	2	0	1	6	126	0	9	0	2	**64**	**93**
Kilinochchi	2	78	0	7	0	0	0	0	0	16	0	7	1	7	0	0	0	0	0	13	1	1	0	0	**22**	**99**
Mannar	1	74	0	6	0	0	0	1	0	0	0	30	0	5	0	0	0	0	0	1	0	7	0	0	**39**	**100**
Vavuniya	2	118	0	5	0	1	0	0	0	0	1	28	0	8	0	1	0	0	0	19	7	10	1	10	**11**	**100**
Mullaitivu	2	106	1	10	0	0	0	3	0	12	0	29	0	5	0	1	0	0	0	12	0	0	0	6	**24**	**100**
Batticaloa	39	2009	3	145	0	7	0	5	0	18	2	69	0	1	0	5	0	1	4	53	0	25	0	1	**59**	**100**
Ampara	5	131	0	2	0	1	0	0	1	1	0	70	0	1	0	1	0	0	1	27	1	25	0	2	**8**	**65**
Trincomalee	13	1930	1	16	0	1	0	0	0	64	0	54	1	15	0	0	0	0	3	41	0	22	0	1	**26**	**99**
Kurunegala	59	2229	0	31	0	8	0	0	0	6	2	243	0	9	0	9	0	2	16	336	5	106	18	317	**24**	**100**
Puttalam	27	2707	1	9	0	2	0	1	0	1	3	42	0	8	0	1	0	0	1	81	3	40	0	16	**22**	**100**
Anuradhapur	13	594	2	8	0	0	0	1	0	2	2	226	1	29	0	3	0	0	7	163	1	35	8	339	**25**	**98**
Polonnaruwa	12	462	1	12	0	5	0	0	4	10	5	136	0	5	0	12	0	0	3	56	0	15	4	259	**35**	**97**
Badulla	40	770	0	26	0	5	0	0	0	32	9	230	4	35	0	68	0	0	2	115	0	32	2	28	**65**	**100**
Monaragala	12	433	0	15	1	6	0	0	0	0	4	407	2	32	0	17	0	1	0	50	2	49	5	119	**27**	**100**
Ratnapura	48	1539	3	32	0	13	0	2	1	15	44	802	0	21	0	13	0	2	7	119	1	111	14	124	**35**	**100**
Kegalle	84	2145	1	17	0	2	0	2	1	11	20	472	2	26	0	4	0	0	12	275	3	46	2	27	**30**	**100**
Kalmune	19	1576	6	50	0	10	0	0	0	0	1	36	0	1	0	0	0	0	3	50	3	25	0	0	**41**	**100**
SRILANKA	1545	51756	28	662	**5**	**116**	**0**	**46**	**10**	**328**	179	5553	**23**	**911**	**0**	**178**	**0**	**12**	11	2967	41	779	**79**	**2023**	**38**	**99**

Source: Weekly Returns of Communicable Diseases (esurvillance.epid.gov.lk). T=Timeliness refers to returns received on or before 21st July, 2023 Total number of reporting units 358 Number of reporting units data provided for the current week: 353 **C****-Completeness

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

Table 2: Vaccine-Preventable Diseases & AFP

15th– 21st July 2023 (29th Week)

Disease	No. of Cases by Province									Number of cases during current week in 2023	Number of cases during same week in 2022	Total number of cases to date in 2023	Total number of cases to date in 2022	Difference between the number of cases to date in 2023 & 2022
	W	C	S	N	E	NW	NC	U	Sab					
AFP*	00	00	00	00	00	00	00	00	00	00	00	50	44	13.6 %
Diphtheria	00	00	00	00	00	00	00	00	00	00	00	00	00	0 %
Mumps	00	00	02	00	01	01	00	01	00	05	00	126	35	260 %
Measles	21	01	00	02	00	01	00	00	01	26	01	88	14	528.5 %
Rubella	00	00	00	00	00	00	00	00	00	00	00	01	00	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	06	05	20 %
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	02	07	- 71.4 %
Whooping Cough	00	00	00	00	00	00	00	00	00	00	00	05	01	400 %
Tuberculosis	77	42	15	21	12	00	05	07	27	206	120	5249	3254	61.3 %

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

Number of Malaria Cases Up to End of July 2023,

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All are Imported!!!

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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