WEEKLY EPIDEMIOLOGICAL REPORT

A publication of the Epidemiology Unit
Ministry of Health

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WEER SRI LANKA 2023

Vol. 50 No. 32 05th– 11th Aug 2023

Human Challenge Trials: Exploring Ethical Considerations and Practical Challenges

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Human challenge studies (HCTs), also known as controlled human infection studies (CHIs), represent a distinctive form of clinical trials where healthy volunteers willingly subject themselves to intentional infection with a pathogen. These trials aim to deepen our understanding of diseases and test the effectiveness of vaccines or treatments. While HCTs have been valuable in advancing medical knowledge and combating infectious diseases for decades, they also raise significant ethical concerns surrounding the risks and benefits for participants.

Both human challenge trials and traditional clinical trials play crucial roles in studying diseases and developing new interventions, yet they differ markedly in their design, purpose, and participant profiles. Clinical trials are primarily focused on assessing the safety and efficacy of interventions in patients with specific diseases or conditions. In contrast, human challenge trials seek to study the disease itself by deliberately exposing healthy volunteers to a pathogen. To ensure participant safety and welfare, both trial types are bound by stringent ethical and regulatory guidelines.

In recent times, human challenge studies have garnered renewed interest as a potential tool to expedite the development of vaccines and treatments for emerging infectious diseases, such as the COVID-19 pandemic. The urgency of the global health crisis has emphasized the critical need for effective medical solutions, prompting consideration of human challenge studies as a means to accelerate testing and approval processes. It is worth noting that these studies extend beyond COVID-19 and are also applied to investigate other infectious diseases like malaria, typhoid fever, and influenza.

In the context of COVID-19, human challenge studies involve deliberately exposing participants to the virus, allowing researchers to closely observe its effects and assess the efficacy of potential treatments or vaccines. While HCTs offer unique advantages in terms of expediency and efficiency, they simultaneously give rise to ethical and practical concerns that demand thoughtful consideration.

History of Human Challenge Studies

Human challenge studies have a long history in medical research, dating back to the 18th century when Edward Jenner conducted the first smallpox vaccine trial by deliberately infecting a young boy with cowpox. Since then, human challenge studies have been used to study a wide range of infectious diseases, including typhoid fever, cholera, malaria, influenza, and dengue fever.

In the early days of human challenge studies, researchers often used themselves as subjects to test new treatments or vaccines. For example, in the 1940s, Thomas Rivers, a virologist at the Rockefeller Institute for Medical Research, infected himself with a strain of the influenza virus to study the disease and develop a vaccine.

Over time, human challenge studies became more formalized and regulated, with strict ethical guidelines and safety protocols. Today, human challenge studies are conducted in specialized facilities that are designed to minimize the risk of infection and ensure the safety of participants.

Ethical Considerations

Human challenge studies raise several ethical concerns, particularly around the risks and benefits for participants. Because these studies involve intentionally infecting

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healthy volunteers with a pathogen, there is a risk of harm, including serious illness or death. This risk is generally higher for diseases that have no effective treatment or vaccine, or for vulnerable populations such as children or pregnant women.

At the same time, human challenge studies have the potential to provide valuable information about the disease and test new treatments or vaccines more quickly and efficiently than traditional clinical trials. This can be especially important for emerging infectious diseases, where time is of the essence in developing effective interventions.

To address these ethical concerns, human challenge studies are subject to strict regulatory oversight and ethical review. In the United States, the Food and Drug Administration (FDA) and the National Institutes of Health (NIH) have established guidelines for the conduct of human challenge studies, including requirements for informed consent, safety monitoring, and risk assessment.

Practical Challenges:

Pathogen Selection: Choosing an appropriate pathogen for HCTs involves considering its virulence, transmissibility, and available treatment options. The selected pathogen should pose a manageable risk to participants while still providing meaningful data.

Participant Selection: Identifying suitable participants who are at low risk of severe complications from the infection is crucial. This requires rigorous screening processes to ensure the safety of participants.

Safety Measures: Implementing strict safety protocols and providing adequate medical care and monitoring during the trial is essential to minimize the risk to participants.

Benefits and Risks

Human challenge studies have the potential to provide valuable information about infectious diseases and test new treatments or vaccines more quickly and efficiently than traditional clinical trials. By intentionally infecting healthy volunteers with a pathogen, researchers can study the disease in a controlled environment and monitor the immune response to the infection.

HCTs can significantly expedite the vaccine development process by providing faster results compared to traditional clinical trials. This is particularly crucial during a pandemic when timely vaccine development is of utmost importance.

HCTs require a smaller number of participants compared to traditional trials, as the controlled environment allows for more precise observations and measurements. This can help conserve resources and reduce costs.

By deliberately infecting participants, researchers can gain valuable insights into the disease's progression, immune response, and potential treatment options. This knowledge can inform the development of more effective vaccines and therapies.

However, human challenge studies also carry significant risks for participants, including the risk of serious illness or death. This risk is generally higher for diseases that have no effective treatment or vaccine, or for vulnerable populations such as children or pregnant women.

To minimize these risks, human challenge studies are subject to strict safety protocols and ethical review. Participants are carefully screened to ensure that they are healthy and at low risk of complications from the infection, and they are closely monitored throughout the study.

Regulatory Frameworks

Human challenge studies are subject to strict regulatory oversight and ethical review to ensure the safety and well-being of participants. In the United States, the FDA and the NIH have established guidelines for the conduct of human challenge studies, including requirements for informed consent, safety monitoring, and risk assessment.

In the United Kingdom, human challenge studies are regulated by the Medicines and Healthcare Products Regulatory Agency (MHRA) and are subject to ethical review by the Health Research Authority (HRA) and the Research Ethics Committee (REC).

Conclusion

Human challenge studies are a valuable tool for advancing medical knowledge and developing new treatments and vaccines for infectious diseases. However, they also raise significant ethical concerns about the risks and benefits for participants.

To address these concerns, human challenge studies are subject to strict regulatory oversight and ethical review, and participants are carefully screened and monitored throughout the study. While human challenge studies are not without risks, they have the potential to provide valuable information about infectious diseases and accelerate the development of effective interventions.

Moving forward, it is crucial to strike a balance between the potential benefits of HCTs and the ethical considerations and practical challenges they present. Robust ethical frameworks, stringent safety measures, and transparent communication with participants and the public are essential to ensure the responsible conduct of HCTs.

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Table 1: Selected notifiable diseases reported by Medical Officers of Health 29th– 04th Aug 2023 (31st 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	282	10620	0	8	0	10	0	1	0	7	10	216	0	0	0	3	0	0	7	193	0	29	0	5	**32**	**100**
Gampaha	247	10849	0	15	0	13	4	7	0	3	6	368	0	7	1	12	0	0	3	183	6	60	0	30	**5**	**100**
Kalutara	80	3571	0	14	0	2	0	0	0	6	8	563	0	1	0	5	0	1	15	323	1	65	0	1	**24**	**100**
Kandy	272	4696	0	27	0	0	0	8	0	15	9	198	2	44	0	3	0	1	3	172	0	18	1	24	**87**	**100**
Matale	45	1074	0	2	0	3	0	1	0	10	4	119	1	13	0	3	0	0	3	39	0	4	6	211	**26**	**100**
NuwaraEliya	6	179	2	96	0	3	0	3	1	43	7	89	2	52	0	4	0	0	5	98	2	11	0	1	**62**	**100**
Galle	73	1824	1	36	0	12	0	5	0	21	19	644	4	37	0	1	0	1	0	225	1	16	0	3	**37**	**100**
Hambantota	18	1150	0	8	0	3	0	1	0	8	1	228	1	56	0	8	0	0	2	106	0	16	5	415	**27**	**100**
Matara	51	1349	0	19	0	8	0	1	0	12	4	403	0	26	0	5	0	2	7	192	0	16	4	126	**55**	**100**
Jaffna	27	1791	9	66	0	2	0	9	0	17	1	10	1	488	0	2	0	1	0	129	0	10	0	2	**65**	**93**
Kilinochchi	1	84	0	7	0	0	0	1	0	16	0	8	0	7	0	0	0	0	0	13	0	2	0	0	**23**	**100**
Mannar	0	77	0	6	0	0	0	1	0	0	0	30	0	5	0	0	0	0	0	2	0	8	0	0	**43**	**100**
Vavuniya	5	128	0	5	0	1	0	0	0	2	0	29	0	8	0	1	0	0	1	20	0	11	0	10	**12**	**100**
Mullaitivu	0	107	0	11	0	0	0	3	0	12	1	30	0	5	0	1	0	0	0	12	1	1	0	6	**24**	**99**
Batticaloa	26	2061	1	151	0	7	0	5	0	18	0	71	0	1	0	5	0	1	8	62	0	25	0	1	**60**	**100**
Ampara	4	197	0	5	0	1	0	1	0	52	2	108	0	2	0	1	0	0	0	56	0	38	0	5	**5**	**100**
Trincomalee	13	1961	2	19	0	1	0	0	0	65	0	55	0	15	1	2	0	0	1	43	3	25	0	1	**27**	**100**
Kurunegala	55	2341	1	32	0	8	0	0	0	6	6	251	0	9	0	9	0	2	15	358	10	126	20	352	**26**	**100**
Puttalam	20	2760	1	10	0	3	0	1	1	2	1	46	0	8	0	1	0	0	1	82	0	44	0	17	**24**	**100**
Anuradhapur	13	619	0	8	0	0	0	1	5	7	0	228	1	30	0	3	0	0	5	175	1	39	15	373	**25**	**99**
Polonnaruwa	11	481	0	12	0	5	1	1	0	10	1	137	0	5	0	12	0	0	0	60	0	16	4	270	**34**	**100**
Badulla	22	827	0	26	0	5	0	0	1	43	6	246	2	39	1	71	0	0	1	118	1	34	0	28	**66**	**100**
Monaragala	12	459	2	17	0	6	0	0	1	1	7	417	0	32	0	20	0	1	0	51	2	51	1	124	**26**	**100**
Ratnapura	51	1643	1	33	0	13	0	2	0	16	23	854	1	23	1	15	0	2	5	132	0	111	0	125	**35**	**100**
Kegalle	72	2288	0	19	0	2	0	2	0	11	7	496	2	30	0	4	0	0	6	290	2	51	2	29	**31**	**100**
Kalmune	11	1607	1	52	0	10	0	0	0	0	2	39	0	1	0	0	0	0	2	57	0	27	0	0	**44**	**100**
SRILANKA	**1417**	**54743**	**21**	**704**	**0**	**118**	**5**	**54**	**9**	**403**	**12**	**5883**	**17**	**944**	**4**	**191**	**0**	**12**	**90**	**3191**	**30**	**854**	**58**	**2159**	**39**	**99**

Source: Weekly Returns of Communicable Diseases (esurvillance.epid.gov.lk). T=Timeliness refers to returns received on or before 04th Aug, 2023 Total number of reporting units 358 Number of reporting units data provided for the current week: 356 **C****-Completeness

Table 2: Vaccine-Preventable Diseases & AFP

29th– 04th Aug 2023 (31st 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	01	01	00	00	00	02	02	56	47	19.1 %
Diphtheria	00	00	00	00	00	00	00	00	00	00	00	00	00	0 %
Mumps	01	00	01	00	01	00	01	01	00	05	06	139	50	178 %
Measles	27	00	00	12	00	00	00	01	00	40	01	164	16	925 %
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 Encephalitis	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	79	06	09	01	11	09	08	13	09	145	124	5575	3520	58.3 %

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

Seek medical advice if you get a fever after exposure to muddy water or soil.

It could be Leptospirosis.

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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