Is India Ready for CHIM studies?

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CHIM – Controlled Human Infection Model – was the topic of discussion at the Media Interaction on CHIM studies at Translational Health Science and Technology Institute (THSTI), an autonomous institute of the Department of Biotechnology, Ministry of Science & Technology, Govt of India, Faridabad, on 17 September 2019.

The possibility of introducing CHIM into research in India is being considered by scientists in order to develop biomedical technologies, including new vaccines. CHIM studies involve measured insertion of an infectious agent into a healthy person to observe the development and progression of a disease and further test for possible treatments such as vaccines against that disease.

Emergence of CHIM

It was on 14 May 1796, when Edward Jenner, English physician and scientist, applied pus from cowpox sore into the cuts on the arm of a healthy boy. Six weeks later, Jenner inoculated the boy with the pus from smallpox sore and found that the boy did not get smallpox. The antibodies developed against cowpox not only made the boy immune to cowpox but he also developed immunity against the smallpox virus. This was the first documented example of a CHIM study, which led to the concept of vaccinations.

In the following years, many challenging studies were conducted for a wide range of diseases, in which participants were intentionally tested (whether or not they were vaccinated) with an infectious disease organism. This was to study how diseases such as malaria and yellow fever were transmitted. CHIM studies since then have contributed immensely to the understanding of infectious diseases.

Understanding CHIM

Similar to what Jenner did, in a CHIM study, a well-characterized attenuated (weakened) strain of an infectious agent is administered in a controlled dose by a specific route of administration into consenting healthy volunteers. Before administering the agent, it is important to know the natural history of the infection, its virulence (the severity of the disease), persistence in the body and the possibility of secondary infection. Also, the strain of the microorganism should be an epidemiologically relevant strain, which is manufactured under 'Good Manufacturing Practice' conditions.

Giving an example, the vaccine to be tested is administered into a small group of human volunteers. Then after a period of time during which the volunteers would have developed immunity, the volunteers are deliberately infected with the pathogen (disease-causing microbe) and are monitored for a specified period. If the vaccine works, the volunteers will not fall ill.

Most important is maintaining the volunteer's safety. In any CHIM study, the volunteers have to be carefully monitored by trained health professionals and scientists, usually for a period of 10-14 days. Following this pre-defined period, volunteers are administered treatment with the infectious agent whether they show signs of the infection or not.

Why opt for CHIM?

Most drugs and vaccines developed to cure infectious diseases are first tested in animals. But the problem here is that for many of the infectious diseases, animal models do not replicate the way the disease progresses in humans. This is why a lot of interventions, which prove promising in animal studies, may not work well in humans. And the time for development of new interventions is lost.

Approval of drugs and vaccines is based on large-scale clinical trials, which involve a large number of people. As compared to CHIM studies, Phase II and III clinical trials require as many as 200,000 volunteers while a CHIM study would require not more than 150 people. This could prevent many people from being subjected to interventions, which are not likely to work. In addition, clinical trials are expensive to conduct. However, CHIM study would need the involvement of skilled scientists, microbiologists, excellent clinical facilities and careful recruitment, monitoring and governance.

The Present Scenario

Until now, around 155 CHIM studies have been registered on ClinicalTrials.gov, a resource provided by the US National Library of Medicine, which gives a database of privately and publicly funded clinical studies conducted around the world. In recent years, CHIM studies have contributed to the development of vaccines for diseases such as malaria. 'Vaxchora', a traveler's vaccine against cholera has been licensed by the US FDA based on a CHIM study.

In 2016, the Oxford Vaccine Group used a CHIM study to evaluate the efficacy of a typhoid vaccine

developed by Bharat Biotech, an Indian company. This vaccine is licensed for use in India, but its efficacy remains to be tested in the Indian population.

Most CHIM studies are being conducted in high-income countries such as UK, US, Netherlands and Denmark. Unfortunately, only 7 per cent of these studies are carried out in lower-middle-income countries (LMIC). In fact, these are the countries where there are endemic pathogens that do not affect populations in more industrialised countries. Countries like Kenya, Gabon, Tanzania and Thailand are now involved with CHIM studies with growing interest from several other countries.

To-date no CHIM study has ever been done in an LMIC before being carried out in high-income countries. The problem is that for many diseases, interventions, which work well in high-income countries, are not as effective in endemic settings. Factors such as exposure patterns, naturally acquired immunity, diet, intestinal microbes, environment, the genetic profile of the host population and many others influence the epidemiology (the incidence, distribution and possible control of diseases and other factors relating to health) of the disease.

CHIM studies carried out in endemic settings, where the disease prevails, for example, in areas where malaria is prevalent, can guide the development of interventions and treatments that are more likely to succeed in people who need such interventions the most.

Should India consider CHIM studies?

Studies report that infectious diseases contribute to about 20 per cent of the disease burden in India. Currently, CHIM studies are not being done in India. The Indian Council for Medical Research (ICMR) approved a CHIM study for malaria in principle. But the expert committee of ICMR solicited for an Indian strain of *Plasmodium falciparum* (one of the parasites that causes malaria) to be used for the study. The study did not go further because *Plasmodium* is difficult to grow and characterisation of the strain would take several years.

World Health Organization (WHO) has recently introduced guidance norms on the use of CHIM for developing new vaccines. Now, since India is a major vaccine manufacturer, there are enough reasons why India should consider such studies. One of which is the local relevance; research pertaining to the disease in endemic areas will be more relevant to the local population. Also, there can be a better understanding of genetics, pre-exposure, immune status and environmental factors.

Scientists aver that CHIM studies would greatly benefit the research enterprise both in terms of scientific development and cost. The procedure for developing a new drug or vaccine presently involves using animal models, which are deliberately infected. This process helps determine the safety and efficacy of the drug or vaccine. And those proven safe products are then tested on human volunteers – clinical trials. Not all diseases have good animal models. For instance, a vaccine that works on a rat may not work on humans. The process of ruling out ineffective vaccine candidates is long.

CHIM could help fast-track drug and vaccine development and testing its efficacy for diseases. It would speed up research at the early stages and would bring down the research cost. It is true that CHIM studies may not be able to replace the usual Phase III clinical trials in the near future, yet products are now being licensed based on CHIM studies, for instance oral cholera vaccine licensed by FDA. Phase III studies are difficult to design especially when disease outbreaks occur and the prevalence is difficult to predict.

Ethical Issues

There is a considerable debate regarding the use of CHIM. The idea of deliberately infecting a human volunteer is obviously alarming. But scientists assure that CHIM studies are well regulated. During the course of the study, volunteers are tested frequently and are treated at the first sign of infection. There have not been any adverse events associated with CHIM studies globally. However, they do raise a debate in the minds of people.

Public engagement, informed consent and volunteer selection are important aspects. The studies require rigorous research protocols and researcher sensitivity while dealing with volunteers. In India and other developing countries, the issue of compensation for lost time, income and transport cost to participants is a tricky one. Money could influence poor people to participate in human infection studies.

Arising from the discussions in the Indian ethics community on using CHIM, healthy, educated adults who are empowered to protect themselves should be allowed to participate in the study. Initially, such studies should be allowed only in high-quality academic institutions. This is to address the issues of trust and protection of research participants. Both researchers and ethics committee that who reviews, permits and monitors these studies would need training.

Convincing people for the benefit of health and medical science is a difficult task for scientists and medical personnel. With all the information available on CHIM studies, it is finally upto the public to make informed decisions.

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