It is indeed a pity that even after death, Henry Molaison was short-changed.

***Note**: The author's review of Dittrich's book has been published in Neurology India (7).*

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Controlled human infection models for vaccine development: Zika virus debate

VIJAYAPRASAD GOPICHANDRAN

Abstract

An ethics panel, convened by the National Institute of Health and other research bodies in the USA, disallowed researchers from the Johns Hopkins University and University of Vermont from performing controlled human infection of healthy volunteers to develop a vaccine against Zika virus infection. The members published their ethical analysis and recommendations in February 2017. They have elaborated on the risks posed by human challenge with Zika virus to the volunteers and other uninvolved third parties and have systematically analysed the social value of such a human challenge experiment. They have also posited some mandatory ethical requirements which should be met before allowing the infection of healthy volunteers with the Zika virus. This commentary elaborates on the debate on the ethics of the human challenge model for the development of a Zika virus vaccine and the role of systematic ethical analysis in protecting the interests of research participants. It further analyses the importance of this debate to the development of a Zika vaccine in India.

Introduction

In December 2016, an ethics panel convened by the US National Institutes of Health (NIH), the National Institute of Allergy and Infectious Diseases (NIAID) and the Department of Defense Walter Reed Army Institute of Research (WRAIR) reviewed a proposal by researchers from the Johns Hopkins University and the University of Vermont College of Medicine in the USA to conduct controlled infection of healthy human volunteers with the Zika virus (ZIKV) to develop a vaccine against the virus. The panel published its recommendations in February 2017, halting the progress of any such experiments, as it deemed such research unethical in the current context of research on and development and understanding of the ZIKV (1). This evoked mixed opinions and led to vociferous debates between the proponents of the controlled human infection models (CHIM) for ZIKV vaccine development and the bioethicists, who view the risks to the participants and other uninvolved third parties as too high to allow the experiments (2,3).

ZIKV is a mosquito-borne flavivirus, causing a febrile exanthematous (fever with rash) illness in humans. Though it was isolated and identified in 1947, the first major human outbreak was only in 2007 in the Island of Yap, in the Pacific (4). In July 2015, Brazil reported an association between ZIKV and Guillain-Barre syndrome (GBS – a severe form of nervous disorder due to immunological problems caused by the ZIKV); and in October of the same year, an association between ZIKV infection of pregnant women and microcephaly (small head) of new-borns with severe neurological damage (4). Most illness caused by ZIKV infection is mild and not apparent. However, its association with GBS and congenital Zika syndrome (CZS) are the major causes for concern. The virus is transmitted by the bite of the *Aedes* mosquito, as well as by sexual transmission and vertical transmission from the mother to the foetus (5). The virus rapidly spread to Mexico, Central America, the Caribbean, and all over South America. Given these concerns and the possibility of the spread of the virus to other tropical and subtropical areas, the World Health Organisation declared the disease a Public Health Emergency of International Concern in January 2016 (4). Since then, the ZIKV has been a dreaded emerging infectious disease, and laboratory research and animal experiments have been conducted to understand

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the virus, and its infectivity, ability to cause serious illness and modes of transmission. Several researchers have also been working on developing vaccines against the virus.

In many experiments in the past, human participants have intentionally been infected with infective agents and the data obtained have been used to advance the understanding of the infective agents and to develop treatments and vaccines against them, from the yellow fever human challenge of 1900 to the more recent dengue human challenge of 2013 (6,7) a human dengue virus challenge model (ie, a controlled live dengue virus infectious challenge study. Miller's and Grady's ethical analysis of human challenge models, published in 2001, provides a reasonable ethical framework for the assessment of these studies (8). However, ethical scholarship has still not been able to come up with a thorough and systematic assessment of the various ethical dimensions of CHIMs. The report and recommendations of the panel assessing the ethical justification of the ZIKV CHIM serves as a comprehensive framework for such an assessment. This commentary will focus on the arguments supporting the use of CHIM to make scientific advances in ZIKV research, the ethical concerns related to the use of CHIM in ZIKV research and finally, the implications of this debate for India.

Why do we need controlled human challenge with Zika virus?

Though the ZIKV has been known for more than 70 years, its exact mechanism of infectivity in humans, pathogenesis and mode of transmission, and the duration of the persistence of the virus in blood and body fluids are not well understood (9,10).* The proponents of CHIM argue that the human challenge models will help us understand the virus in greater detail. The other strong argument in favour of CHIM is that it would help to advance the development of a vaccine. Routine field trials for a vaccine would depend on natural infections in the community and an assessment of the extent of protection of the vaccinated group as compared to the unvaccinated. This is likely to take time as it is dependent on the natural infectivity of the virus. On the other hand, CHIM would drastically bring down the time and cost of the studies by introducing the virus into vaccinated and unvaccinated persons and observing for infections and immune response (11). The CHIM provides opportunities for research and development even in areas with low ZIKV endemicity and during periods when the epidemic wanes and the transmission of the virus in the community is low (12). Moreover, CHIM experiments with the dengue virus in recent years have been successful, posing minimal risks to the participants (13). On the basis of these arguments, the researchers proposed that such a human challenge study is essential for understanding the ZIKV, as well as for being prepared with vaccines and therapeutic agents in case of a pandemic. Against this background, the ethics panel commissioned by the NIH, NIAID and WRAIR performed a systematic analysis of the justification for such a controlled human challenge with ZIKV and the conditions for its ethical acceptability.

Ethical challenges in using CHIM for vaccine against ZIKV

Risks of controlled ZIKV infections for the participants

Though in most cases, the ZIKV infection is mild and not apparent, the infected participants will suffer from fever, rash, body pains, headache and tiredness for a period ranging from 2 to 7 days (14). The major risks associated with ZIKV infection are GBS, other neurological complications such as myelitis (spinal cord infection), encephalitis (brain infection), optic neuritis (infection of nerve of the eye), and congenital Zika syndrome, in which the foetus of an infected mother suffers from severe brain damage (9).* The incidence of GBS among ZIKV-infected patients has been reported to be about 2.5–3.0 per 10,000 and it affects mostly those over 60 years of age (15). GBS has been associated with severe neurological morbidity, and sometimes even mortality. The occurrence of such immune-mediated neurological damage has also been reported to be higher among persons who have been previously immunised against or infected with another flavivirus, such as dengue and chikungunya. More recently, ZIKV has been isolated from the kidneys and testes of mice (16). However, we do not have a good understanding of the extent of renal damage and male infertility caused by the virus. Moreover, there is no definitive treatment and since effective interventions are not possible, the level of risk becomes greater. This is in stark contrast with the other controlled human challenge experiments for the development of vaccines, eg, against the dengue virus, in the recent past. Before the controlled human challenge experiments were allowed, the characteristics of the dengue virus were well known and the risks and harms well understood (13). It was also possible to develop and isolate the strain of the dengue virus that causes the least harm to infected volunteers.

Risk of controlled ZIKV infection for third parties

The ZIKV has been shown to be transmitted by the bite of the *Aedes* mosquito, from mother to foetus, through sexual contact and through blood transfusion (5). Therefore, there is a risk that a volunteer infected with the virus may transmit it to his/her contacts through any of these modes. This would subject third parties who are not in the know to the risks of ZIKV infection. We do not know much about the duration for which the viraemia persists. In some cases, persistent viraemia of up to 90 days has been documented and, therefore, the duration of infectivity through sexual contact and vertical transmission is likely to be prolonged (17,18). Hence, strict and long-term contraception may be required to prevent mother-to-foetus transmission and long-term protection may be required to prevent sexual transmission. The volunteers may find the burden of such prolonged isolation, contraception and sexual protection rather too high.

The social value of experimental CHIM with ZIKV

Several questions arise with respect to the social value of the use of CHIM with ZIKV(19). First, does a CHIM make it more likely for researchers to obtain information on the virus and

its characteristics that is not already known? There are not enough pre-clinical studies of ZIKV infection (10). Adequate animal models and pre-clinical laboratory experiments are required before the human challenge to ensure that enough is known about the virus and its effects. Second, does the CHIM design help in bridging this gap in knowledge? The CHIM includes infecting the human volunteers by injecting the ZIKV, which is an artificial mode of infection. This may not lead to clinical manifestations similar to the actual modes of transmission, such as mosquito bites. Moreover, strains of ZIKV which produce the milder form of illness have still not been isolated and cultured, thus precluding the possibility of creating milder infections among all volunteers. Therefore, the design is less likely to lead to realistic findings, and more likely to create greater than minimal harm. Third, does understanding the characteristics of the virus and developing a vaccine using the CHIM have an impact on medicine or public health? Definitely, the development of a safe and effective ZIKV vaccine would have a great public health impact. The CHIM would reduce the time required for the development and approval of a vaccine. Therefore, there is social value in terms of the accelerated development of a vaccine. Fourth, research and development agencies working on the ZIKV vaccine should have substantial commitment to the task of ensuring that the findings of the human challenge experiment enhance and advance their respective research, thus driving the need for the CHIM (12). In other words, different stakeholders should ensure good coordination of research initiatives so that the results of the CHIM may lead to substantial advancement in the development of a vaccine. This condition would strongly support the case for conducting the CHIM. Finally, are there other less burdensome methods to understand the virus and advance the development of a vaccine than a CHIM, or is a CHIM the best option? A CHIM may be useful in understanding several characteristics of ZIKV infection, such as the incubation period and period of viraemia. However, such information may not be essential for the development of a vaccine. Developing an effective vaccine against ZIKV infection is possible without a CHIM, as in previous trials for the development of a virus vaccine. However, a CHIM might substantially accelerate the development of a vaccine – by as much as two years – which is a very important gain, given the looming threat of the ZIKV pandemic (11). Lastly, the most important reason for which the human challenge is the best option is that even in areas with low endemicity and areas where the epidemic force has waned, research and development could be continued in this area if CHIM were allowed, whereas in the absence of CHIM, field experiments would be extremely difficult in such circumstances (11). Therefore, the balance between the social value and the risks is very delicate.

The NIH, NIAID and WRAIR ethics panel also laid down some key ethical conditions under which such a CHIM may be permissible. These are protection of vulnerable populations; a robust, informed consent process; adequate compensation, but not undue inducement, for volunteers; respect for the right to withdraw from the study; independent expert review other than the routine ethical oversight; mechanisms for compensation for research-related injuries; and active community engagement in the research (1).

Relevance of this debate to India

India is an active party in the debate on the ethical permissibility of CHIM for the development of a ZIKV vaccine. Bharat Biotech Private Limited, a biotechnology start-up in Hyderabad, has announced that it has developed two vaccines against ZIKV and has filed patents. It has begun phase 1 clinical trials of the inactivated ZIKV vaccine (20). If it decides to conduct Phase II and III trials of these vaccines in India, where ZIKV is still not widely prevalent, it may have to resort to CHIM experiments. The current Indian government's policy is strongly tilted towards "make in India", whereby entrepreneurs and start-up companies are encouraged to manufacture in India (21). Considering this policy environment and the excitement of potentially being the first company in the world to develop a ZIKV vaccine, it is likely that the vaccine trials may be speeded up. Given that such a CHIM may be rolled out, it is important to assess the situation in India.

The Ministry of Health and Family Welfare, Government of India, reported the first three cases of ZIKV infection from Ahmedabad, Gujarat, in May 2017. These indigenous cases were identified through laboratory-based and hospital-based surveillance. The ministry has responded to this report by establishing an inter-ministerial task force to closely monitor the status of ZIKV infection. Information on ZIKV infection and its transmission is being displayed at international airports. The Integrated Disease Surveillance Programme is actively looking out for outbreaks of acute febrile illness for the early identification of ZIKV outbreaks. The Indian Council of Medical Research has started surveying thousands of human and mosquito samples for ZIKV (22). The identification of cases of ZIKV infection in India has opened up a serious threat and poses important ethical concerns regarding CHIM of ZIKV in India. The risk posed by ZIKV CHIM is extremely high in the Indian context as the virus is currently not widespread in the country (23). Dengue and chikungunya are endemic in India and outbreaks of dengue are common during the rainy months in several parts of the country. People who live in areas endemic to dengue and chikungunya run a high risk of contracting ZIKV infections. Moreover, people who have serological immunity to these other flaviviruses have been shown to be more susceptible to the immune-mediated complications of ZIKV infection, such as GBS. Under these circumstances, CHIM trials can lead to serious complications among the Indian population. Establishing methods of long-term strict isolation, ensuring long-term sustained contraception, and interrupting sexual transmission to prevent the risks to non-participants may all be challenges in the Indian setting. The cost of establishing and maintaining these safeguards may be prohibitive.

An important question to be considered if the ZIKV vaccine trials were allowed in India is whether the approved vaccine

would be available, accessible to the poor, and affordable for all. Some of the mandatory requirements specified by the ethical panel for allowing a CHIM, such as ensuring a robust process of informed consent, protecting vulnerable participants and ensuring compensation for research-related injuries, may be difficult to achieve in a setting like India, where the capacity for ethical oversight of research is still inadequate.

In conclusion, the debate on the ethical feasibility of controlled human challenge for developing the ZIKV vaccine has been very instructive insofar as understanding ethical considerations in human challenge experiments is concerned. The ethical panel's decision to disallow the human challenge experiment for a ZIKV vaccine has reinforced the importance of thorough ethical oversight of research and development at a global level. The role of an ethical review as a system of checks and balances to keep fast-paced research within limits can never be overemphasised (24). It is the role of ethical review to ensure protection of research participants in the existing scientific and social context. The ethics panel served this purpose by systematically assessing the landscape of ZIKV research and making sure that the CHIM is not allowed till more is known about the virus, and more protections are in place.

Such ethical review and analysis panels are important for creating a sound discourse on the ethics of various new technologies and developments in health in India. The field of ethical review of health interventions should be systematically strengthened by building the capacity of health policy-makers, providers and managers. Reviews by expert panels will enhance ethical discourse and help build capacity. Before allowing CHIM for ZIKV vaccine development in India, there is a need to set up an expert panel comprising of virologists, immunologists, infectious disease experts, public health experts, ethicists, health systems experts and policy makers to evaluate the current landscape of ZIKV infection in the country. Such an expert panel should evaluate the social value of the CHIM experiments and should assess the potential and capacity of research units to carry out the CHIM without serious adverse consequences. The expert panel should also ensure that appropriate ethical guidelines are developed for such CHIM experiments in a unique socio-cultural context like India.

(****Corrections***: Some extraneous text appearing in Columns 1 and 2 on page 52 was deleted on January 7, 2017.)

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Issues in access to end-of-life care in low-resource areas

YOGESH JAIN, GAJANAN PHUTKE

Abstract

Even though 1% of people require palliative and end-of-life care in low-resource situations, it remains an uncharted arena. Yet it is as important as curative care to alleviate suffering. Palliative care is not only a need in cancer and HIV disease; but is needed in a diverse group of illnesses ranging from tuberculosis, renal failures, paraplegia to chronic lung diseases. In a lower resource setting, the gaps in palliation may be the need for more technology and interventions or more healthcare professionals. Thus, palliative care will initially mean ensuring that life-prolonging treatment that most patients do not get is ensured to them. It is morally unacceptable to focus on comfort care as an alternative to advocating for patients' rights for appropriate life-prolonging treatments. If organised well and standard protocols are developed to support health workers, appropriate care can be provided for all people. Ethical principles of autonomy, non-maleficence and benevolence will have to guide this development. We will have to prioritise for high value care which means choosing cheaper alternatives that are just as effective as more expensive diagnostic or therapeutic modalities. There is a need to settle the priorities between palliative and disease-modifying or curative treatments. Major roadblocks that limit access of the rural poor to palliative care relate mainly to the misconceptions among policy-makers and physicians, large gaps in health worker training and cultural mindsets of care-providers. A specific example of misplaced policies and regulations is the poor availability of opiates, which can make end-of-life care so much more dignified in illnesses that have chronic pain or breathlessness. A three-tiered structure is proposed with a central palliative care unit which will oversee several physicians and specially trained nurses for non-communicable diseases, who will oversee primary healthcare centre-based nurses, who in turn, will oversee village health workers.

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Introduction

Effective, affordable palliative care or end-of-life care remains unavailable to most people in rural areas (1) either because there is scarcity of physicians who are too busy pursuing curative intent or because the system has abandoned patients with no cure (2,3) leading to the prolonged agony of many.

In marginalised villages of India, one finds so many people with incurable illnesses where the health system they accessed for care has given up on them. These illnesses span different specialties from oncology to pulmonary to infectious diseases to neurological conditions. Patients often have multiple morbidities, for example:

- A patient with HIV infection with multi-drug resistant (MDR) pulmonary tuberculosis (TB) complicated by major adverse effects on the second-line MDR regimen, who has given up on drugs and is not ready to continue with the DOTS plus centre.
- A patient with post-tubercular bronchiectasis and fibrothorax with frequent chest infections, severe malnutrition, charpoy-bound, and slowly wasting away.
- Oxygen-dependent lung disease in a severely kyphoscoliotic person.
- A person with D5-D6 spinal cord injury after a motorcycle accident resulting in paraplegia and requiring chronic indwelling urinary catheter.
- A patient with lepromatous leprosy with frequent type 2 ENL reactions with limb slowly wasting away due to a non-healing trophic ulcer despite MDT for 2 years.
- A person with chronic psychosis with schizophrenia, who runs away from home, has frequent violent episodes, with exhausted family members.