**TITLE: Ethical challenges posed by CHIMS studies in endemic settings**

**Review Comments:**

Comments of Reviewer 1;

1. The argument that human challenge studies are not only permissible, but are also ethically required, rests on the grounds that vaccines and drugs are the only way to control the infection. In case of infections like dengue, Zika, malaria etc. it shifts focus from environmental modifications and vector control to vaccines and drugs. In case of diseases like cholera and enteric fever, the argument seems to place greater emphasis on vaccine and treatment than social determinants such as hygiene, sanitation, safe water etc.
2. Under the section “Human Challenge Studies” the authors make some very important arguments. One more argument that needs to be considered here is – Is an artificial challenge with a controlled strain of the infective organism, similar to a wild type of infection? Is the response to vaccines and the susceptibility to the new drug treatment similar for both the controlled infection and the wild natural infection? For example, it has been described that Zika virus infection through injection of a controlled strain is very different from the infection through a mosquito bite. In such a case, how can a controlled infection model be equated to a natural infection?
3. The authors make a statement “Though numerous infamous historical cases of unethical research involved the intentional infection of human subjects with pathogens(6, 7), the (sparse) existing bioethical ethical discourse on modern HCS(1, 8-14) appears to reflect consensus that intentional infection of human research participants *per se*is not ethically unacceptable—whereas grossly unethical challenge studies of the past were wrong for other reasons” - This statement needs more clarification. How do the authors conclude that such a consensus exists? The Zika controlled infection model was disallowed in the US based on strong ethical reasoning.
4. If presence of an effective treatment is a pre-condition for controlled infection models, how will it serve the purpose in case of neglected diseases which do not have effective treatments yet?
5. The authors make a statement that “HCS participants in endemic settings may in some cases thus directly benefit from immunity gained from a less severe bout of illness than otherwise would have been likely and/or required for them to gain immunity” - In many infectious diseases immunity thus acquired wanes after a period of 5 – 10 years. This phenomenon would only serve to shift the susceptible age. It can be dangerous in case of diseases which when occurring in childhood are innocuous but may be highly virulent when they occur in older age, such as chicken pox or Hepatitis A. Therefore, this argument needs to be carefully re-evaluated.
6. The contamination of the sewage with the challenge strain also raises concerns of alterations in the genetic profile of the infective agent in the environment.

Comments of Reviewer 2:

Review comments:

1. *As the authors note, there have been growing calls for more human challenge studies (HCS) to be conducted in endemic settings, and there are good scientific and ethical reasons to consider conducting more such studies.  However, both HCS in general, and in particular HCS in low- and middle- income countries (LMIC) where neglected diseases are often endemic, raise a number of important ethical challenges.  This paper provides a useful summary of the main features of HCS and the ethical challenges associated with their conduct in LMIC settings.*  
  
2. *Being an overview of the key issues to consider in an accessible format, there is some potential for it to influence policymakers with their decision-making in relation to HCS research in endemic settings.*

*3. The key scientific and ethical issues posed by HCS in endemic (LMIC) settings have been covered before, but insofar as this is an overview of the key issues to consider in an accessible format, I think it is a useful paper to include in a special journal issue on this topic.*

*4. Insofar as this is an overview of the key issues, I don’t think there are any important omissions.*

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