Ethical and Practical Issues Associated With the Possibility of Using Controlled Human Infection Trials in Developing a Hepatitis C Virus Vaccine

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Despite the existence of established treatments for hepatitis C virus (HCV), more effective means of preventing infection, such as a vaccine, are arguably needed to help reduce substantial global morbidity and mortality. Given the expected challenges of developing such a vaccine among those at heightened risk of infection, controlled human infection studies seem to be a promising potential approach to HCV vaccine development, but they raise substantial ethical and practical concerns. In this article, we describe some of the challenges related to the possibility of using controlled human infection studies to accelerate HCV vaccine development. The related ethical and practical concerns require further deliberation before such studies are planned and implemented.

Keywords. challenge studies; controlled human infection studies; ethics; hepatitis C virus; vaccines.

Despite established curative treatments for hepatitis C virus (HCV), better means of preventing infection are arguably needed. An estimated 71 million persons worldwide have chronic HCV infection, which can lead to cirrhosis, hepatocellular carcinoma, and death [1]. The incidence of HCV infection has risen dramatically in young people who use drugs, children born to mothers with active HCV infection, and men with human immunodeficiency virus (HIV) infection who have sex with men [2–4]. Transmission through unsafe medical practices and transfusion remains unacceptably high in many places in the world [5, 6]. In high-income settings, most new HCV infections are due to injection drug use; and in the United States (US), the opioid crisis has led to a doubling of incident HCV since 2010 [7, 8]. Because HCV can be transmitted by percutaneous exposure to contaminated blood, programs to reduce incident HCV infection have focused on attenuating unsafe injections, unscreened blood donations, and high-risk injection drug use. While safer injection and sex practices as well as treatment of substance use disorder reduce HCV incidence, effective delivery of harm reduction tools has been challenging in many settings, largely due to widespread lack of access to proven harm reduction strategies [5, 6].

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Treatment with oral direct-acting antiviral medications (DAAs) can lead to cure in > 95% of those treated, resulting in reduction in liver disease mortality and transmission of HCV to others [9]. In small, well-defined populations, such as HIV-infected men who have sex with men (MSM), high rates of curative HCV treatment have lowered HCV incidence [10]. However, HCV treatment as prevention is significantly more challenging in other populations for whom diagnosing HCV and linking those infected to treatment is more difficult (eg, persons who are homeless and those who inject drugs) and among whom HCV reinfection following curative therapy is probably due to ongoing heightened risk of infection [11].

Despite the relatively short period of observation in the current HCV treatment era, relatively high rates of HCV reinfection occur in persons actively injecting drugs and MSM living with HIV [12]. In British Columbia, Canada, 40 incident HCV reinfections were detected among 4114 individuals treated with DAAs [12]. While medical treatment of opiate use disorder reduced the rate of reinfection, substance use disorder is a chronic condition with periods of relapse that may result in HCV reinfection years after curative therapy. For example, of 94 people who had previously used injection drugs, but were abstinent at the time of HCV cure who were followed over 7 years, 37 (27%) relapsed to injection drug use and 10 were reinfected with HCV [13]. Similarly, 24% of MSM cured of HCV via DAAs were reinfected within 2 years [14].

Incident HCV infection and reinfection represent major challenges to reaching the World Health Organization's (WHO) goal of HCV elimination by 2030, which necessitates a 90% reduction in new HCV infections [6]. In 2016, nearly 60% of surveyed countries had more infections than cures and few

countries were on target to achieve HCV elimination by 2030. In a 2018 survey of 45 high-income countries, only 11 were on target to achieve the WHO's incident HCV infection reduction goal [15]. In the US, the Centers for Disease Control and Prevention reports that HCV incidence has increased each year since 2010 to 1.04 cases per 100 000 population in 2017 [16].

In this setting, more durable means of HCV prevention are needed. Models have demonstrated that achievable coverage levels of a low-efficacy prophylactic HCV vaccine could greatly reduce HCV transmission among people who inject drugs (PWID) and provide significant additional prevalence reduction beyond treatment alone [17, 18]. Accordingly, a safe and effective vaccine would be extremely welcome and likely cost-effective option for helping to control HCV [1]. However, developing such a vaccine raises a complex set of scientific, practical, and ethical challenges among populations at risk. After describing some of these challenges, we examine the possibility of using controlled human infection studies to accelerate HCV vaccine development along with their potential benefits and pitfalls.

LIMITATIONS OF HUMAN HCV VACCINE TRIALS AMONG POPULATIONS AT RISK

Vaccine efficacy is difficult to assess without a population at predictably high risk for infection where the results are interpretable. Rates of HCV transmission among MSM can be high, but the highest-risk MSM are either at high risk of HIV acquisition as well or are already living with HIV [19]. This is problematic since testing vaccines in an HIV-infected population may underestimate immunogenicity. In contrast, the incidence of HCV infection in HIV-uninfected PWID is predictably high (5%–25% per year), pinpointing PWID as a vaccine test population as well as underscoring the continued need for prevention of HCV infection in this population [20].

Some cohorts of PWID have achieved successful identification, enrollment, and prospective monitoring to enable testing an HCV vaccine [21–29]. Unfortunately, trials with PWID present practical and ethical challenges. For example, the close follow-up that is necessary to establish vaccine safety and efficacy can be difficult because of the strong association of injection drug use with multiple social vulnerabilities, including homelessness, food insecurity, and illegal activities that result in incarceration [30]. In addition, the numerous medical consequences of drug injection complicate assessments of safety. Furthermore, the ethical conduct of a trial in which participants are at risk for infection requires that risk-reduction techniques be employed. While these strategies are variably successful, prevention trials for other infections, such as HIV, have experienced a decline in incidence compared to the baseline population following enrollment. When incidence declines, the duration of follow-up or the number of enrolled subjects must be increased to observe the number of infections needed to detect a vaccine effect. Thus,

the time and expense of completing a trial also increases due to effective risk-reduction strategies, potentially preventing trials from being launched and thereby extending the time until a safe and effective vaccine is available. Many of these issues were manifest in the only prophylactic HCV vaccine efficacy trial completed to date (ClinicalTrials.gov identifier NCT01436357): The incidence of infection was lower than predicted, which resulted in the trial taking > 5 years to complete; there were many adverse events not related to vaccine administration; and the vaccine did not meet efficacy endpoints. At present, there are no other prophylactic HCV vaccines in phase 2 or later stages of testing, demonstrating that rapid development of an HCV vaccine is highly unlikely without a different strategy.

POTENTIAL ADVANTAGES OF CONTROLLED HUMAN INFECTION STUDIES FOR HCV VACCINE DEVELOPMENT

In controlled human infection studies, sometimes referred to as challenge studies, carefully selected healthy adult volunteers are exposed to a well-characterized strain of an infectious agent in order to understand human diseases or to test vaccines or other treatments. Controlled human infection is a method used extensively in testing vaccines against a variety of pathogens.

For example, in malaria vaccine development, many experts consider controlled human infection studies ethically required rather than just permissible [31]. Since < 10% of preclinical vaccine candidates progress to phase 3 clinical evaluation, many vaccine candidates must be tested to obtain safe and effective vaccines [32]. Even in settings with a high incidence of infection, pathogen exposure does not occur in all vaccinated subjects. In those without evidence of infection, it can be difficult to distinguish lack of exposure from complete protection by the vaccine. In controlled human infection studies, every vaccinated subject is exposed to the pathogen. Exposure that occurs in a controlled setting with healthy volunteers maximizes safety, assessments, and access to prompt medical care as needed. Controlled human infection studies have reduced the number of large-scale malaria vaccine trials fielded in malaria-endemic areas, which entail barriers to treatment and medical care [33]. In addition, it is likely that controlled human infection studies have minimized human exposure to ineffective vaccines.

The scientific and practical issues associated with HCV vaccine development suggest the importance of considering the use of controlled human infection studies. Not only would they offer the possibility of careful and more expeditious scientific assessment, but they should also help attenuate the risks of onward transmission that might be associated with conducting vaccine trials among those at risk.

Furthermore, well-designed controlled human infection studies seem to have substantial social value given the promise of a vaccine to mitigate substantial morbidity and mortality due to HCV and its sequelae [1, 34, 35]. While at such an early stage

of development, it is impossible to forecast accurately how a safe and effective HCV vaccine would be implemented in different settings; a vaccine should provide a more durable means of protection than any other available methods of prevention currently available, regardless of risk factor. Similar arguments based in social justice have been elaborated in the pursuit of a preventive HIV vaccine, despite the availability of effective means of prevention and treatment [36] and pertain here. The contours of both epidemics and the challenges of consistently providing access to preventive measures are tightly analogous. Furthermore, although vaccines can be morally controversial for some, they can be widely implemented across jurisdictions varying in economic status.

Additionally, the lack of a robust animal model for HCV infection lends support to justifying HCV controlled human infection studies. Currently available in vitro systems and immunocompetent small animal models permit very limited assessment of whether vaccine-induced adaptive immune responses will provide protective immunity against HCV [37]. The only nonhuman animal naturally susceptible to HCV infection is the chimpanzee. While research with chimpanzees played a significant role in understanding the immune response to HCV, their use in invasive laboratory research is no longer permitted [38]. Thus, humans are the only population in which HCV vaccines can be tested for efficacy.

Finally, while most persons with acute HCV infection are expected to be asymptomatic, research participants with clinically concerning findings could be rapidly treated with DAAs. Studies of these medications in persons with acute HCV infection have demonstrated excellent safety, tolerability, and efficacy [39]. Of particular relevance are studies of transplantation. In one study, 20 HCV-uninfected adults underwent kidney transplantation with organs from HCV-infected donors; all recipients developed acute HCV infection and, despite surgery and immunosuppressive drugs, achieved HCV cure with antiviral medications [40, 41]. Successful outcomes have also been reported in persons infected with HCV during liver, lung, or heart transplantation with HCV-infected organs. Such studies provide strong support for the hypothesis that iatrogenic, acute HCV infection can be effectively cured with antiviral therapy.

SELECTED ARGUMENTS AGAINST CONTROLLED HUMAN INFECTION STUDIES WITH HCV

Despite their potential benefits in accelerating vaccine development and testing, controlled human infection studies always raise ethical concerns. After all, these studies would involve intentionally exposing a healthy subject not only to a pathogen, but also to a vaccine candidate. Consequently, there have been substantial ethical deliberations about controlled human infection studies in general as well as for particular pathogens. While it is beyond the scope of this article to review this literature in detail, one useful summary captures a key set of issues that

should be considered when determining the ethical appropriateness of a controlled human infection trial. These include the need for (1) a scientific rationale; (2) the absence of an superior alternative; (3) informed consent; (4) an assessment of benefits and harms; (5) selection of study participants; (6) independent review; (7) publicly available rationale; (8) protection of the public; and (9) compensation for harm [32]. More recently, in the wake of discussions about the potential use of human challenge studies involving Zika virus, two additional criteria have been described: verification that bystander risks be minimized and the determination that there is substantial social value [42]. While each of these criteria would need to be satisfied in the context of a particular HCV controlled human infection study, these studies face several difficulties specific to HCV that argue against using such an approach. We consider these in turn.

First, exposing humans to HCV in controlled human infection studies will be constrained by current limitations in the ability to culture the virus. Existing culture strains of HCV have adaptive mutations that enhance replication efficiency in vitro with unknown effects in humans. Additionally, this culture strain would not represent the complex mixture of genetically distinct, but closely related variants (referred to as a "quasispecies") that circulate in infected humans. Attenuated forms of some pathogens, such as dengue virus, are used to minimize the risk of controlled infection. However, it is not currently possible to generate or propagate attenuated HCV. Because of these limitations related to culturing and attenuating HCV, exposing subjects to the virus might require infusion of infected human plasma that may be coinfected with other unknown pathogens. Despite taking measures to try to mitigate the associated risks, such as obtaining plasma in settings where other copathogens are less likely and testing for known pathogens such as HIV, it is unlikely that no other viruses will be transmitted or that all the implications of infusing plasma from an HCV-infected human into a healthy volunteer are clear. It is also unclear whether direct infusion of HCV-infected human plasma would completely recapitulate natural exposure in terms of infectious dose or other characteristics of natural infection. Last, the HCV infused should ideally have demonstrated sensitivity to drugs used to treat HCV, which might suggest the need to require that the plasma specimen be obtained from a patient who was later cured of HCV infection.

Second, controlled human infection studies testing an HCV vaccine candidate will need to be of a long duration, which has implications for the appropriate treatment of participants and perhaps their sexual partners. A safe and effective HCV vaccine need not prevent infection to prevent disease because it is chronic infection with HCV that causes almost all the associated morbidity and mortality. About 75% of those infected develop persistent infection. Of the 25% who spontaneously control infection, about 85% of them will do so in 6 months. Thus, the actual meaningful outcome of infection is not known

for 3–6 months following infection, and follow-up needs to be extended beyond that point to capture adequate data about whether an infected subject will clear infection or become persistently infected. As a result, the duration of trials of HCV vaccines designed to decrease the rate of chronic infection is quite long. While some professional guidelines recommend deferral of HCV treatment in the acute phase of HCV infection to allow for spontaneous clearance, current US HCV guidance specifies that persons with acute HCV should be treated immediately to reduce the risk of onward HCV transmission [43, 44]. In addition, the emerging global consensus that treatment in the acute phase of infection is indicated could make trials that last for months more difficult to support. During the 4–6 months of observed viremia, there is a risk of infection of others, such as sexual partners. Accordingly, this risk needs to be included in the informed consent process, and how the potential harms to participants' partners will be managed should be explicitly outlined in the study protocol and reviewed by the responsible research ethics committee. Nonetheless, the risk of onward transmission is expected to be substantially lower in controlled human infection studies than would be expected in trials conducted with PWID due to the relative ease of transmission via blood. Therefore, immediate treatment might be less important in this context since the benefit of early HCV cure is generally not realized by individuals with acute HCV infection and exceptions could be incorporated to provide treatment for symptomatic volunteers [45].

Third, women and men will need to be enrolled in HCV vaccine trials despite potential concerns of HCV transmission to fetuses. Women are more likely than men to clear HCV infection spontaneously [46–48], so vaccine safety and efficacy data from both women and men are essential. While enrolling both women and men also comports with ethical and regulatory mandates to include both women and men in research, enrollment of those who may become pregnant raises concerns about the potential for the transmission of HCV to unborn children. Consequently, it will be essential to address concerns related to contraception as trials are designed and implemented, including during the consent process.

Fourth, similar to experience with HIV vaccine trials, stigma associated with HCV and problems with insurability may be encountered [49]. Beyond the stigma of simply being enrolled in an HCV controlled human infection study, participants could become anti-HCV antibody positive. This may have implications for insurability. A related consequence will likely be a restriction on blood donation for those participants who are inclined to do so. Regardless, such possibilities must be meaningfully incorporated in the consent process.

Fifth, testing in healthy volunteers will not negate the need for subsequent testing in at-risk populations. Controlled human infection studies can identify the best candidate vaccines to advance to trials in those at risk, but given the failure of such a study to replicate all the conditions of natural human infection, final vaccine candidates are not likely to be approved for use until they demonstrate they reduce natural transmission or progression to chronic infection. In addition, approved vaccines will ultimately have to be administered to those at highest risk of infection to have the most immediate impact, which argues for conducting later-stage research among those at risk. Similar challenges have been described for other vaccines [50–52]. Such trials will require substantial preparedness work [30].

CONCLUSIONS

Widespread access to treatment and a preventive vaccine likely represent the best strategy to control HCV regardless of risk factor on a global scale. Given the challenges of developing such a vaccine among those at heightened risk of infection, controlled human infection studies are a promising potential approach to HCV vaccine development, yet they raise substantial ethical and practical concerns that require further deliberation before they are planned and implemented. Such deliberation should involve key stakeholders including scientists, those affected by HCV, regulators, ethicists, and insurers. We hope the issues described in this article offer a springboard for these deliberations. The final goal is developing a safe, effective, and durable means of preventing HCV such as a vaccine, which promises to alleviate substantial global morbidity and mortality.

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