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Will There Be a Vaccine to Protect Against the Hepatitis C Virus?

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The discovery of the hepatitis C virus (HCV) more than 20 years ago offered the promise of a vaccine to prevent life-long persistent infection and associated progressive liver diseases. To date, only a few candidate vaccines have been tested in human beings for safety and immunogenicity. None have yet been assessed for prevention of HCV infection or persistence. In the event that current vaccine candidates do not advance to efficacy trials, or fail to provide protection against HCV, the pipeline of alternatives appears to be very small. With a sharp reduction in new HCV infections because of effective screening of the blood supply, and the possibility that acute and chronic infections will be curable because of improving therapy,¹ it is reasonable to ask if the considerable effort to develop a preventive HCV vaccine still is needed. The answer is almost certainly affirmative. Vaccines that protect against hepatitis A and B virus infections were first targeted to health care workers. The value of adding a vaccine to prevent accidental HCV infection in the workplace is clear.

A preventive HCV vaccine would have a far greater impact on public health. The need is highlighted by a concerning increase in new infections among adolescents and young adults recently observed in Massachusetts. Between 2002 and 2009, confirmed HCV cases shifted from a unimodal to bimodal age distribution because infection rates increased among those aged 15–24 years, however, they continued to decline among older adults.² The increase in new HCV infections in the younger age group is attributable to needle sharing and probably will be confirmed elsewhere in the United States and in other countries. Without a preventive vaccine it will be difficult to contain a smoldering epidemic of unrecognized HCV infections involving those who are least likely to seek or receive antiviral therapy, no matter how effective. A vaccine also would be highly beneficial in regions of the world with high HCV endemicity, for instance, in countries such as Egypt where it has proved difficult to interrupt several decades of HCV transmission by standard public health measures.³ When considering the need for a vaccine, it is important to remember that symptoms of acute hepatitis are often mild or inapparent, therefore years can elapse before infection is recognized and treated. Serious liver disease can develop during that time and the infection remains transmissible to others by high-risk practices. Perhaps as importantly, only a very small percentage of HCV infections were ever treated with pegylated type I interferon and ribavirin.⁴ New direct-acting antivirals will improve this situation, but only with a much greater effort to diagnose the large number of unrecognized infections and provide access to costly treatment that must be managed carefully to prevent emergence of resistant viral variants.

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Conflicts of interest

The authors disclose no conflicts.

How to Vaccinate Against HCV Infection?

HCV infection resolves spontaneously in some human beings and chimpanzees,⁵ the only species other than human beings with known susceptibility to the virus. Successful control of infection is associated with a sustained adaptive immune response.⁵ This provides a strong rationale for the development of a preventive HCV vaccine. At the same time the challenge of vaccination is underscored by frequent persistence of the virus owing to mutational escape from humoral and cellular immunity and functional exhaustion of the HCV-specific T-cell response.⁵ Current candidate vaccines prime HCV-specific CD4+ T cells, an important component of protective immunity because early failure of the helper response is a defining feature of infections that persist.⁵ Candidate vaccines differ, however, in the type of effector immune response they generate. Neutralization of HCV infectivity to prevent or alter the course of infection is the primary objective of antibody vaccines. They generally are comprised of HCV envelope glycoproteins formulated as recombinant of proteins with adjuvants, produced as virus-like particles, or expressed from plasmid DNA vectors.⁶ Other vaccines are designed to generate CD8+ T-cell immunity, mostly using the HCV core or nonstructural proteins that are better conserved between genotypes than the envelope glycoproteins targeted by antibodies.⁶ The goal of these T-cell vaccines is to prevent HCV persistence, but not necessarily infection. In support of this approach, convalescent chimpanzees and human beings are susceptible to re-infection, but the second infection usually resolves more rapidly and persists less frequently when compared with primary infection in nonimmune individuals.^{7,8} The importance of cellular immunity in protection from persistence was proved by transient antibody-mediated depletion of CD4+ helper or CD8+ cytotoxic T cells from immune chimpanzees just before rechallenge with HCV. Infection was prolonged or persisted in animals depleted of these T-cell subsets.^{9,10} The burden of HCV-related disease in human beings is associated with long-term chronic viral replication and very rarely with the acute phase of the infection. Conceding that acute-phase virus replication is acceptable if the infection resolves is an entirely new paradigm, quite different from that of other licensed viral vaccines.

The protective effect of several antibody and T-cell vaccines has been assessed in chimpanzees. There have been successes and some apparent failures of both approaches.¹¹ Informative trends emerged when 13 published studies were analyzed collectively. This meta-analysis highlighted an impressive suppression and/or delay in peak acute-phase viremia in animals, regardless of whether they received an antibody or T-cell vaccine. Antibody vaccines may provide a better outcome as defined by prevention of persistence.^{11,12} In many of these studies apparent sterilizing immunity was observed in some chimpanzees, but so far only against closely matched viruses belonging to the same HCV genotype. Cross-genotype protection from persistence has been observed in animals with natural immunity to HCV because of prior infection,⁷ but whether vaccine-induced antibodies or T cells provide the same broad protection has not yet been tested. This is an important issue because there are at least 6 major HCV genotypes that show 25%–30% divergence, and considerable genetic diversity also is observed within genotypes.¹³

Two vaccines that showed promise in chimpanzees have advanced to human trials. One is a prototypical antibody vaccine ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00500747) NCT00500747) containing recombinant envelope glycoproteins E1 and E2 from a genotype 1 virus. Phase I testing in human volunteers documented strong antibody responses that neutralized infectivity of other genotype 1 viruses,¹⁴ and also a genotype 2 virus with reduced efficiency.¹⁵ CD4+ T-cell proliferative responses also were detected, as expected.¹⁴ The T-cell vaccine evaluated in human beings was comprised of 2 serologically distinct recombinant adenovirus vectors that expressed only nonstructural HCV proteins ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01070407) NCT01070407). A prime-boost regimen generated impressive levels of CD4+ and CD8+ T-cell immunity,¹⁶

equivalent to those that suppressed acute-phase virus replication in vaccinated chimpanzees.¹⁷ Whether these vaccines prevent persistence in human beings has yet to be tested but, if effective, would be a tremendous accomplishment. Even in an era of improved antiviral therapy, such a vaccine would provide an important primary layer of protection for health care workers and others at risk of occupational exposure to the virus.

Universal immunization of the general population may be needed to protect those with infection risk that is identified less easily. Whether current antibody or T-cell vaccines will be compatible with this goal could be questioned. Current vaccines are complex from a technical point of view. Optimal neutralizing antibody responses are generated only when recombinant HCV envelope glycoproteins are precisely folded to preserve epitope conformation. Genetic vaccination to elicit long-lasting CD8+ T-cell immunity may require priming and boosting with different vectors. Combining these approaches should provide the best protection against HCV persistence, but at the expense of a further increase in vaccine complexity. It also may complicate deployment to regions of the world where the virus is endemic, especially if matching of vaccine antigen(s) to the dominant circulating HCV genotype(s) is required. Technological advances eventually may solve these problems. Methods to study cellular entry and antibody-mediated neutralization of HCV have improved tremendously in a short period of time.¹⁸ Progress toward design of a vaccine that promotes antibody-mediated neutralization of heterologous HCV genotypes and subgenotypes has been described.^{15,19,20} Adjuvants that deliver recombinant proteins to the class I processing pathway for CD8+ T-cell induction also might hold promise. The challenge of this approach is highlighted by very preliminary studies of one such adjuvant, the Iscomatrix (CSL, Melbourne, Australia). Some human beings developed CD8+ T-cell immunity when immunized with recombinant nonstructural HCV proteins formulated with the iscomatrix adjuvant.²¹ This vaccine also sharply suppressed acute-phase virus replication in chimpanzees (Michael Houghton, personal communication). However, viremia ultimately persisted in 4 of 5 vaccinated animals but in none of the mock-vaccinated controls. Why infection persisted in more of the vaccinated animals is not clear, but the experiment suggests that caution is necessary when advancing vaccine candidates to human trials.

Should Alternate Approaches to Vaccination Be Considered?

Vaccinating most or all of the population against HCV would be feasible if the combination of cost, ease of production, and distribution was similar to that of other vaccines that are used widely in developed and developing countries. The hepatitis A virus and hepatitis B virus (HBV) vaccines offer a prime example of how near-universal use in some countries has changed public health. If universal vaccination against HCV is to be realized, a simpler alternative that does not require priming of neutralizing antibodies and/or CD8+ T cells may be needed. One pathway forward could involve vaccination to prime CD4+ T cells, without a specific effort also to generate effector immune responses. The minimum requirements for induction of cytotoxic T cells, antibodies, and T helper cells by vaccines are compared in Figure 1. Antigens that elicit CD4+ T-cell immunity are comparatively easy to produce, for instance, with the recombinant DNA technology used to manufacture the HBV surface antigen vaccine. Recombinant nonstructural viral proteins such as NS3 that are rich in epitopes targeted by CD4+ T cells would be well suited for class II processing and presentation without any requirement to maintain native conformation. Multivalent vaccines incorporating non-structural proteins of different HCV genotypes could provide relatively broad protection against infection. The antigen composition of such a vaccine also would be substantially easier to reconfigure when compared with recombinant envelope antigens and viral vectors, for instance, to address a substantial shift in the prevalence of HCV genotypes in a geographic region, as illustrated by increasingly common HCV genotype 4 infections in

Europe.²² Some features of HCV infection favor protection by a vaccine designed primarily to elicit CD4+ T cells. There is an unusually long 8- to 12-week lag between HCV infection, generation of cellular and humoral immunity, and initial control of viremia. This provides a wide window for an accelerated, vaccine-primed, CD4+ T-cell response to coordinate and promote successful effector (ie, antibody and CD8+ T cell) responses. Mutational escape of the virus also is less common for the CD4+ T-cell response than antibody or CD8+ T-cell responses,²³ although evasion of vaccine-induced helper responses remains a possibility.²⁴ Finally, frequent spontaneous resolution of infection in chimpanzees that received adjuvanted recombinant envelope proteins may hint at a protective role for CD4+ helper T cells.^{11,12} It is plausible that vaccine-mediated protection from persistence was not caused solely by the antibodies against the envelope glycoproteins, but instead by a high-quality CD4+ T-cell response.

Risks and challenges in the development of a vaccine to prime CD4+ T cells also must be acknowledged. For instance, the choice of adjuvant could determine the success or failure of a vaccine-primed, CD4+ T-cell response, and whether accelerated, functional antibody and CD8+ T-cell responses follow as a consequence of HCV infection. Whether vaccine-induced CD4+ T-cell memory is durable, or is susceptible to failure during acute hepatitis C, also is unknown. From a practical standpoint, the common chimpanzee (*Pan troglodytes*) remains, for the foreseeable future, the only animal model to evaluate vaccine-mediated protection from persistence. Most preclinical studies to assess protection by candidate HCV vaccines were conducted at primate research centers in the United States by American, European, and Asian sponsors. The necessity of this research very recently was considered by the Institute of Medicine of the US National Academy of Sciences. Although the Institute of Medicine report provided no specific recommendation on the need for chimpanzees in HCV vaccine research, it did indicate that studies should be permitted only when there is no alternative, or to prevent significant delays in progress that would be detrimental to human health.²⁵ The impact of these guidelines on HCV vaccine research is yet to be determined. It is important to note, however, that some candidate vaccines did not advance to human trials because they failed to protect or modify the course of HCV infection in chimpanzees. Whether the successful candidates would have advanced to human trials without evidence that they provided protection against HCV challenge in animals is not known. The difficulty of human trials to prove that candidate vaccines reduce, and do not increase, the frequency of HCV persistence cannot be overstated. There are few well-characterized cohorts suitable for evaluation of candidate HCV vaccines,²⁶ in part because the primary risk factor for infection is now needle sharing associated with illicit drug use. Surrogate markers to predict vaccine effectiveness also are lacking. Finally, a trend toward initiation of antiviral treatment when infection first is diagnosed will complicate analysis of candidate vaccines designed to prevent persistence.

Will There Be a Vaccine for the Hepatitis C Virus?

Antibody and T-cell vaccines have generated immune responses in human beings that are similar to those that protected some chimpanzees from HCV persistence in preclinical studies. Much could be learned about correlates of protective immunity by efficacy trials of these vaccines. Importantly, if the rate of HCV persistence is reduced, we will have a needed vaccine for those with a clearly identifiable risk of infection, most obviously occupational exposure to the virus. Most new HCV infections will occur because of high-risk behavior that is not easily identified or predicted. Vaccination of the general population against HCV may be necessary if the upward trajectory of HCV infection among adolescents and young adults is to be changed. For HCV, a vaccine that protects virus-specific CD4+ T cells from failure early in infection might be sufficient to prevent persistence. More attention to the nature of the CD4+ T-cell response generated by HCV infection, why it often fails, and how

it can be protected by vaccination is needed. A vaccine against HCV could provide substantial momentum toward control of chronic liver disease globally, especially if combined successfully with the licensed HBV vaccine. It also would provide a foundation for eradication of HCV because there is no known reservoir for the virus other than human beings. It should be acknowledged that even if a vaccine does afford protection, universal immunization to reduce the number of new HCV infections worldwide would have a long time horizon. This task is complicated also by a poor understanding of the molecular epidemiology of HCV infection in many parts of the world.²⁷ Better surveillance almost certainly would further strengthen the case for universal vaccination against HCV, aid in the design of vaccines matched to circulating viruses, and perhaps facilitate the development of cohorts needed to assess vaccine efficacy. Without this effort, however, it is difficult to envision how the substantial morbidity and mortality associated with 200 million cases of chronic hepatitis C will be reduced.

Biographies

Abbreviations used in this paper

HBV	hepatitis B virus
HCV	hepatitis C virus

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Figure 1.

Chronic hepatitis C is characterized by functional exhaustion of CD8⁺ T cells and poor neutralization of contemporaneous viruses by antibodies. Failure of these effector immune responses is almost certainly a consequence of inadequate CD4⁺ T-helper cell activity. Why CD4⁺ T-cell responses are not sustained, leading to HCV persistence, is unknown. Candidate HCV vaccines that advanced to human trials elicited effector CD8⁺ T cells or neutralizing antibodies, and CD4⁺ T-helper cells required to generate and sustain these effector responses. Here, we propose that a vaccine to prime CD4⁺ T cells alone will be simpler to design and produce. They also should skew the outcome of most HCV infections from persistence to resolution. It is predicted that effector immune responses will develop naturally as they do in infections that resolve spontaneously, but aided by a strong and sustained vaccine-primed CD4⁺ T-cell response that is much less likely to fail. The antigen requirements and cellular processing pathways that must be engaged for each vaccine type are indicated.