Vaccination at the forefront of the fight against hepatitis B and C

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Vaccination is a key intervention for the elimination of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections to fulfill the WHO’s 2030 global elimination goal. Innovations in 2021 promise to curb HBV transmission by reducing mother-to-child transmission and enhancing vaccine immunogenicity in at-risk adult groups. Additionally, an HCV vaccination trial was conducted, and there were also advances in our understanding of the immunology underpinning the lack of protection against HCV reinfection.

Elimination of hepatitis B virus (HBV) requires robust interruption of mother-to-child transmission and better vaccines to ensure safe and effective seroprotection against HBV for all adults. The majority of individuals infected perinatally develop a persistent infection, where the immune responses fail, leading to future tissue damage and eventual potential for life-threatening complications. This fact underpins the importance of the availability and affordability of effective vaccines and innovative approaches, particularly in low-income and middle-income countries (LMICs). An important example is in sub-Saharan Africa, with HBV accounting for at least 87,000 deaths and with ~350,000 neonates infected at birth annually.

In 2021, in an innovative approach, Thompson et al. explored the feasibility of adding HBV screening and antiviral therapy of pregnant women infected with HBV as well as the monovalent HBV birth-dose vaccination to the existing HIV antenatal maternal and child health-care facilities in the Democratic Republic of the Congo. They demonstrated effectiveness of this two-pronged method in prevention of mother-to-child transmission, with high acceptability among pregnant women (>80%). Among the 4,016 women screened for hepatitis B surface antigen (HBsAg) at routine prenatal care registration, 109 women were positive for HBsAg, and, of those, 90 women were enrolled at a median gestational age of 19 weeks and included in the study analysis. Nine women with high viral loads received antiviral therapy (tenofovir disoproxil fumarate (TDF) 300 mg/day) from between 28 and 32 weeks of gestation until 12 weeks post-delivery. Only 68% of infants born received a birth-dose vaccine, and, of these, 77% received a timely birth-dose vaccine (within 24 hours of birth); despite this somewhat suboptimal vaccine delivery, no HBV mother-to-child transmission was recorded. Notably, all infants were born inside health facilities, which is likely a requirement for this approach and highlights the importance of promoting deliveries in health-care settings in LMICs. The high acceptability of pregnant women to this approach suggests that integration of HBV testing and treatment within existing well-structured HIV facilities, particularly in sub-Saharan Africa, would not increase stigma and discrimination and would indeed increase the uptake of HBV testing and active measures to interrupt mother-to-child transmission of HBV.

Other integrative advances to improve adult vaccination uptake include utilizing the platforms for COVID-19 immunization, but more innovations are required to improve the HBV vaccine’s immunogenicity. Vesikari et al. identified key challenges in the vaccination of vulnerable adult populations and designed a large study (PROTECT) with broad geographical distribution to determine whether immune responses to two additional HBV antigens would improve responses compared with standard HBV mono-antigenic vaccines. They also assessed the seroprotection rate (SPR) after two-dose TAV (a tri-antigenic recombinant HBV vaccine) schedule, compared with the standard three-dose MAV (mono-antigenic yeast-derived alum-adjuvanted vaccine) schedule, which might improve compliance. Notably, older individuals with chronic conditions are usually not enrolled in vaccine clinical trials or in catch-up vaccination programmes. Vaccination of adults is an often overlooked unmet need in public health efforts to eliminate new HBV infections. TAV, containing the small, medium and large HBsAg, demonstrates rapid response and high SPR after two doses in healthy young adults. It is a vaccine with a 20-year history of safe and effective use in the prevention of HBV in Israel in both children and adults. These data are corroborated by phase III results of the PROTECT trial, published in 2021, documenting the immunogenicity and safety of three doses of HBV TAV (796 individuals) compared with the MAV (811 individuals) in adults aged >18 years. TAV was superior to MAV, generating higher SPR 4 weeks after the third vaccination in adults aged 45 years or older. The findings showed that more robust immunogenicity is achievable with TAV, highlighting its potential use in adults, including those with chronic conditions. This study along with another phase III study (CONSTANT; NCT03408730) could have a critical role in elimination of HBV in this missed population (Fig. 1).

Vaccines are also critical for HCV. Despite remarkable progress in HCV therapeutics with the development of direct-acting antivirals (DAAs), new infections continue to outpace cures, highlighting the need for an HCV vaccine. Beyond the enormous diversity of HCV, which has thwarted vaccine design efforts, the challenges of carrying out a study to assess the efficacy of an HCV vaccine candidate are formidable. Although the top-line results from the first human HCV vaccine trial, published in 2021, were disappointing, Kimberly Page, Andrea Cox and colleagues should be congratulated for the tour de force effort required to design, carry out and complete this trial.

Key advances

- In the Democratic Republic of the Congo, combining hepatitis B virus (HBV) screening and treatment for pregnant women, as well as infant birth-dose immunization, with existing platforms for prevention of mother-to-child transmission of HIV, has proven practical and been widely accepted.
- A multicentre, randomized controlled trial demonstrated that the tri-antigenic HBV vaccine elicited a robust immune response in people aged >45 years, including those with chronic disease and an impaired immune response.
- A phase I/II randomized trial evaluated two consecutive hepatitis C virus (HCV) vaccines in adults with a history of injection drug use; the vaccine regimen produced HCV-specific T cell responses but did not prevent chronic HCV infection.
- Transcriptomic data from a cohort treated with direct-acting antivirals revealed a molecular signature of T cell exhaustion in HCV-specific CD8 T cells that remained as a chronic ‘scar’ even after chronic antigen stimulation was stopped.
The vaccination strategy used a recombinant chimpanzee adenovirus 3 vector and a modified vaccinia Ankara virus, both expressing non-structural HCV proteins, as a prime-boost approach. In the phase I/II double-blind study, 548 individuals without prior HCV infection but with a history of injection drug use were randomized to vaccine or placebo and followed for incident HCV infection. In total, 455 participants (228 vaccine and 227 placebo) received both doses. In both groups, 14 participants developed chronic HCV infection, indicating no protection against initial or chronic infection with the vaccine. Although the final outcome was not optimal, there were key lessons from this trial. The vaccine was immunogenic, leading to HCV-specific T cell responses in 78% of those who received the vaccine compared with 3% in the placebo arm. Interestingly, the geometric mean peak HCV RNA level post-infection was lower in the vaccine group (152.51 × 10^3 IU per millilitre and 1,804.93 × 10^3 IU per millilitre, respectively), and reassuringly the vaccine was well tolerated with no safety concerns.

Clearly, an HCV vaccine is a very tall order. Despite promising preclinical data in chimpanzees and generation of an immune response that limited HCV viraemia, the vaccine did not prevent infection or promote spontaneous clearance. Perhaps more importantly, this trial was an enormous undertaking that took 6 years to complete in a challenging population to recruit and follow-up. Repeating this type of effort for each vaccine candidate is not feasible, raising the prospect of new approaches, including using a controlled human infection model (CHIM) of HCV to rapidly test vaccine candidates. Although ethical, virological and logistical challenges must be overcome, the CHIM approach might be a critical tool for vaccine development.

Indeed, data from Hensel and colleagues highlight the significant immunological challenges that HCV presents for vaccine development. Chronic HCV infection promotes pronounced T cell exhaustion. Detailed single-cell transcriptomic data show that HCV clearance with DAAs leads to polarization of HCV-specific CD8+ T cells towards a memory-like phenotype with loss of terminally exhausted CD8+ cells. However, the profile of the memory-like cells did not change after treatment-induced clearance and was clearly distinct from the profile of patients who spontaneously cleared their infection, indicating the presence of an ‘immunological scar’ despite viral clearance. These data suggest that antigen elimination alone is not enough to reverse exhaustion once chronicity is established and might support early treatment during acute infection. Not only does this explain the lack of protection against HCV reinfection after DAA cure of chronic HCV, but it raises concerns that vaccination of previously infected individuals might be particularly challenging owing to persistence of HCV-specific CD8+ T cells that expand to produce only terminally exhausted T cells.

For HCV, effective delivery of existing and simplified vaccines should be a global priority. For HCV, the first vaccine trial was a huge achievement but only highlighted the immense challenges that remain. Understanding the immunology, and considering novel approaches such as CHIMs, will be required if we are going to succeed in developing this key tool in global elimination efforts.

Fig. 1 | Advances in HBV vaccination in 2021. a | Integrating hepatitis B virus (HBV) screening and treatment for pregnant women, as well as birth-dose vaccination, into existing facilities for prevention of mother-to-child transmission of HIV. b | A multicentre, randomized controlled trial (PROTECT) of TAV (a tri-antigenic recombinant HBV vaccine) versus MAV (mono-antigenic yeast-derived alum-adjuvanted vaccine). HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen.