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Randomized Trial of a Vaccine Regimen to Prevent Chronic HCV Infection

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Abstract

BACKGROUND—A safe and effective vaccine to prevent chronic hepatitis C virus (HCV) infection is a critical component of efforts to eliminate the disease.

METHODS—In this phase 1–2 randomized, double-blind, placebo-controlled trial, we evaluated a recombinant chimpanzee adenovirus 3 vector priming vaccination followed by a recombinant modified vaccinia Ankara boost; both vaccines encode HCV nonstructural proteins. Adults who were considered to be at risk for HCV infection on the basis of a history of recent injection drug use were randomly assigned (in a 1:1 ratio) to receive vaccine or placebo on days 0 and 56. Vaccine-related serious adverse events, severe local or systemic adverse events, and laboratory adverse events were the primary safety end points. The primary efficacy end point was chronic HCV infection, defined as persistent viremia for 6 months.

RESULTS—A total of 548 participants underwent randomization, with 274 assigned to each group. There was no significant difference in the incidence of chronic HCV infection between the groups. In the per-protocol population, chronic HCV infection developed in 14 participants in each group (hazard ratio [vaccine vs. placebo], 1.53; 95% confidence interval [CI], 0.66 to 3.55; vaccine efficacy, −53%; 95% CI, −255 to 34). In the modified intention-to-treat population, chronic HCV infection developed in 19 participants in the vaccine group and 17 in placebo group (hazard ratio, 1.66; 95% CI, 0.79 to 3.50; vaccine efficacy, −66%; 95% CI, −250 to 21). The geometric mean peak HCV RNA level after infection differed between the vaccine group and the placebo group (152.51×10^3 IU per milliliter and 1804.93×10^3 IU per milliliter, respectively). T-cell responses to HCV were detected in 78% of the participants in the vaccine group. The percentages of participants with serious adverse events were similar in the two groups.

CONCLUSIONS—In this trial, the HCV vaccine regimen did not cause serious adverse events, produced HCV-specific T-cell responses, and lowered the peak HCV RNA level, but it did not prevent chronic HCV infection. (Funded by the National Institute of Allergy and Infectious Diseases; ClinicalTrials.gov number, NCT01436357.)

Hepatitis C virus (HCV) infection remains one of the most prevalent blood-brone viral infections worldwide and is a leading cause of death from infectious disease globally.[1–3] Despite high cure rates with direct-acting antiviral therapies, more than 71 million people live with chronic HCV infection, and an estimated 1.75 million new infections and approximately 400,000 deaths from HCV infection occur annually.[1–3] From 2009 through 2018, the incidence of HCV infection tripled in the United States, fueled by increases in opioid injecting.[4] Failure to prevent new HCV infections is the leading threat to the World Health Organization 2030 global elimination goal.[2,5,6] A prophylactic HCV vaccine would provide an essential tool for achieving elimination goals by interrupting transmission.[7,8]

We assessed a heterologous prime–boost vaccination strategy with chimpanzee adenovirus 3 (ChAd3) and modified vaccinia Ankara (MVA) vectors encoding the nonstructural proteins (NS) of HCV genotype 1b (ChAd3-NSmut and MVA-NSmut, GlaxoSmithKline). In phase 1 testing, this vaccine regimen had a clinically acceptable safety profile and induced T-cell responses.[9,10]

The primary objectives of this trial were to assess the safety of ChAd3-NSmut and MVA-NSmut when administered to HCV-uninfected persons at high risk for infection and to determine whether the vaccine regimen would be more effective than placebo for the prevention of chronic HCV infection. The secondary objective of the trial was to evaluate the vaccine immunogenicity.

METHODS

TRIAL DESIGN AND PARTICIPANTS

We conducted this phase 1–2 double-blind, randomized, placebo-controlled trial between 2012 and 2018 at Johns Hopkins University; the University of California, San Francisco; and the University of New Mexico. Participants were healthy HCV-uninfected adults (18 to 45 years of age) who had injected drugs within 90 days before randomization. After 68 participants had been enrolled, the data and safety monitoring board recommended that phase 2 be initiated. Participants received risk-reduction counseling and referrals to substance-use treatment and syringe services at every study visit. All participants who acquired HCV infection were referred to independent physicians for clinical follow-up, including HCV treatment evaluation. The trial did not provide or pay for HCV treatment, which national guidelines did not uniformly recommend during acute infection at the time, or obtain treatment data after trial follow-up ended.

HCV-uninfected persons who inject drugs were randomly assigned to receive intramuscular injections of ChAd3-NSmut vaccine (2.5×10^{10} viral particles) on day 0 and MVA-NSmut vaccine (1.8×10^{8} plaque-forming units) on day 56 (vaccine group) or saline placebo on days 0 and 56 (placebo group). Randomization was performed in a 1:1 ratio and was stratified according to sex and *IFNL3* genotype, because both factors alter the likelihood of progression to chronic HCV infection.[11,12] Both ChAd3-NSmut and MVA-NSmut encoded NS3, NS4, NS5A, and NS5B from the HCV 1b genotype with an inactivating mutation introduced in the catalytic site of the HCV polymerase.[9]

Inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. The data and safety monitoring board reviewed interim analyses with a focus on safety, immunogenicity, and recruitment milestones for power and sample-size requirements. The trial investigators were unaware of the randomization assignments and results throughout the trial. Participants were followed monthly for HCV infection for 20 months after enrollment and for 9 months after HCV detection.

OVERSIGHT

The trial was performed in accordance with federal and local ethical standards under an Investigational New Drug protocol. The trial protocol (available at NEJM.org) and trial documents were reviewed and approved by human subjects review committees at Johns Hopkins University; the University of California, San Francisco; the University of New Mexico; the National Institute of Allergy and Infectious Diseases (NIAID); and the Food and Drug Administration. A certificate of confidentiality was obtained to further protect sensitive participant data. Written informed consent was obtained from all participants after a comprehensive explanation of the nature and risks of the trial and successful completion of a comprehension assessment.

Okairos, a company acquired by GlaxoSmithKline, provided the prime and boost vaccines and saline placebo, as well as consultation for the trial. Representatives from GlaxoSmithKline reviewed the protocol and contributed to the writing of the manuscript

that was submitted, including reviewing before submission. Data analyses were conducted by the Emmes Company. The trial sponsor (the NIAID) and the trial principal investigators (the first and last authors) vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, and the principal investigators and lead statistician (the sixth-to-last author) vouch for the data analyses.

EVALUATIONS OF SAFETY

Safety analyses included all participants who received the first injection of vaccine or placebo. The primary safety end points were vaccine-related serious adverse events occurring at any time during the trial period, severe local or systemic solicited adverse events occurring during the 8 days after each injection, and laboratory adverse events assessed at baseline and 1 month after each injection. Participants recorded their body temperature and the presence and intensity of postinjection adverse events daily for 8 days after injection of vaccine or placebo (see Section 2 in the Supplementary Appendix). Laboratory evaluations included monthly white-cell and platelet counts and hemoglobin, alanine aminotransferase (ALT), and creatinine levels; laboratory adverse events are defined in Table S2. All women underwent urine pregnancy testing at screening and before each injection of vaccine or placebo. Pregnant participants were not given vaccine or placebo.

EVALUATIONS OF EFFICACY

Participants underwent monthly qualitative HCV RNA testing by means of transcription-mediated amplification (Gen-Probe). Positive results were confirmed by quantitative HCV RNA and genotype testing in the Johns Hopkins University laboratory[13] or at Quest Diagnostics. Incident HCV infection was defined as a confirmed positive HCV RNA test after a previous negative HCV RNA test (or tests). The date of HCV infection was defined as the midpoint between the last negative and first positive HCV RNA tests.

The primary efficacy end point was chronic HCV infection, defined as persistent viremia for 6 months. Chronicity is established in most infected persons by then.[14] Persistent viremia was defined as the presence of the same virus (confirmed by sequencing of the HCV core–E1 region and phylogenetic analysis) in blood obtained at the first visit in which HCV RNA was detected and at month 6 after incident infection, with a third HCV RNA–positive sample identified between the two visits. An independent expert in HCV sequence analysis compared sequences at the time of incident infection and at later time points to confirm infection with the same virus.[13] An end-point review committee, the members of which were unaware of the randomization assignments, reviewed all cases to confirm the infection end point.

The date of viral clearance was defined as the midpoint of the interval between the last test with detectable HCV RNA and the first of two consecutive tests with undetectable HCV RNA. Exploratory efficacy analyses included assessments of whether the vaccines had an effect on the incidence of (primary) HCV infection, the incidence of chronic HCV infection for 9 months, the geometric mean peak HCV RNA level after infection, the duration of HCV viremia in participants in whom incident HCV infection was cleared, and the incidence of chronic infection with HCV of genotype 1 as compared with non–genotype 1 infection.

MEASUREMENT OF VACCINE IMMUNOGENICITY

T-cell responses were measured by interferon-γ enzyme-linked immunosorbent spot (ELISpot) assays at baseline (before any injection was received) and at 30 and 56 days after the first injection (ChAd3-NSmut or placebo), as well as at 7 and 34 days after the second injection (MVA-NSmut or placebo). Assays were performed with thawed peripheral blood mononuclear cells (PBMCs) and peptide pools derived from the HCV virus used in the vaccine.[9] A positive immune response was defined as more than 48 spot-forming cells per million PBMCs and at least three times the mean background number of spots per million PBMCs. Participants were defined as having had a response to the vaccine or placebo if they had tested negative for HCV-specific immune responses at baseline and had a positive immune response to at least one peptide pool detected after either injection.

STATISTICAL ANALYSIS

Sample-size calculations were based on the detection of a 60% lower incidence of 6-month chronic HCV infection among vaccine recipients than among placebo recipients in the per-protocol population. We calculated that 43 chronic infection events would provide 85% power to detect such a difference with a two-sided logrank test conducted at an alpha level of 0.05. The incidence of chronic infection among placebo recipients was assumed to be 14% annually; thus, a total of 292.5 participants in the per-protocol population followed for 1.5 years would provide, on average, 43 events. Under the assumption that 65% of enrolled participants would be retained in the per-protocol population, the target enrollment was originally estimated as 450 participants. Subsequently, a protocol-specified blinded interim analysis for the reestimation of sample size was reviewed by the data and safety monitoring board, and because of a low incidence of chronic infection, the enrollment target was increased to 540 participants.

Efficacy analyses were performed in modified intention-to-treat and per-protocol populations. The primary efficacy analysis was performed in the per-protocol population; a secondary efficacy analysis of chronic HCV infection was performed in the modified intention-to-treat population. The modified intention-to-treat population included all participants who received the first injection, were HCV negative at the time of the first injection, and had sufficient follow-up data (at least three clinic visits after the second injection). The per-protocol population included participants who met the criteria for the modified intention-to-treat population, received both injections, and had no major protocol deviations that would compromise the assessment of vaccine efficacy. Because the efficacy analyses were time-to-event analyses, data from participants who underwent randomization were included at the point at which the protocol definition of the efficacy end point was met or were censored at the point at which at least one of the analysis population criteria was no longer met, whichever came first. Data from participants who discontinued participation in the trial early or who completed the trial without an observed end-point event were censored at the final visit.

The between-group difference in the incidence of 6-month chronic HCV infection (primary end point) was calculated from the hazard ratio of Cox proportional hazards models, stratified according to sex and *IFNL3* status. Vaccine efficacy was calculated as 100×(1-

hazard ratio). The methods used to assess primary and exploratory end points are described in Section 3 in the Supplementary Appendix. The immunogenicity analysis population included participants who received any vaccine or placebo and for whom immunogenicity end-point data were available.

Safety data were coded according to *Medical Dictionary for Regulatory Activities* preferred term and system organ class and were summarized on both on the participant level and the event level.

Because the statistical analysis plan did not include a provision for correcting for multiplicity for the secondary or other end points, the results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals were not adjusted for multiplicity, so they should not be used to infer definitive treatment effects for the secondary or other end points.

RESULTS

TRIAL POPULATION

A total of 991 persons were screened, and 548 were enrolled. Of the enrolled participants, 78% were male, 61% were White, 21% were Black or African American, and 14% were Hispanic. Sex, race, ethnic group, *IFNL3* status, age, and body-mass index did not differ substantially between the groups (Table 1). The most common reason for not passing screening was not being deemed in good health by a trial physician and having clinical laboratory values outside the acceptable range (103 participants). Among the 548 enrolled participants, 274 (50%) were randomly assigned to the vaccine group and 274 (50%) to the placebo group; 1 participant who had been randomly assigned to the placebo group was erroneously given vaccine for both doses and is included in the vaccine group in all summaries and analyses. A total of 546 participants received the first injection of vaccine or placebo, and 455 participants received both injections (228 in the vaccine group and 227 in the placebo group). Table S3 shows the reasons for discontinuation of receipt of injections and early discontinuation of participation in the trial.

In total, 75 participants became HCV-infected during follow-up (37 participants [13%] in the vaccine group and 38 [14%] in the placebo group) and 2 participants in the vaccine group received treatment for acute HCV infection outside the protocol. A total of 36 participants met the definition of having 6-month chronic infection — 19 (7%) in the vaccine group and 17 (6%) in the placebo group — and the infection was cleared in 9 participants (5 in the vaccine group and 4 in the placebo group), with no evidence of viremia at 6 months (Fig. S1). The numbers of the remaining participants who became infected (including the number who discontinued participation early or completed the trial without an observed end-point event) and the timing of the initial and chronic infections and infection genotypes are provided in Table S4.

VACCINE EFFICACY

No evidence of vaccine efficacy was detected in the primary per-protocol analysis of 6-month chronic infection, in which 202 participants (73%) in the vaccine group and

199 participants (73%) in the placebo group were followed to chronic infection or trial completion and data from the remaining participants were censored before trial completion. A total of 14 participants in the vaccine group and 14 participants in the placebo group were chronically infected at 6 months (Table 2). There was no evidence of vaccine efficacy in the analysis of the incidence of chronic HCV infection in the vaccine group and the placebo group (hazard ratio [vaccine vs. placebo], 1.53; 95% confidence interval [CI], 0.66 to 3.55; vaccine efficacy, −53%; 95% CI, −255 to 34) (Fig. S2). No evidence of vaccine efficacy was detected in the modified intention-to-treat analysis, with 19 participants in the vaccine group and 17 participants in the placebo group chronically infected at 6 months (hazard ratio, 1.66; 95% CI, 0.79 to 3.50; vaccine efficacy, −66%; 95% CI, −250 to 21).

EXPLORATORY EFFICACY ANALYSES

Results of the exploratory analyses of efficacy end points are provided in Table S6. There was no evidence of a vaccine effect on the incidence of chronic HCV infection at 9 months, the incidence of primary HCV infection (14.1 cases per 100 person-years of observation in the overall trial population), the time from incident infection to spontaneous viral clearance, or the incidence of chronic HCV infection with genotype 1 as compared with non–genotype 1 virus. In the placebo group, the geometric mean HCV RNA level increased after incident infection, peaking 1 month after incident infection (Table S7). In the vaccine group (both the per-protocol and modified intention-to-treat populations), the geometric mean peak HCV RNA level occurred at the time of incident infection; the ramp-up of viremia that follows incident infection in natural infection was not observed.[15,16] In the modified intention-to-treat population, the geometric mean peak HCV RNA level was lower in the vaccine group than in the placebo group (152.51×10^3 IU per milliliter [95% CI, 33.5×10^3 to 686×10^3] vs. 1804.93×10^3 IU per milliliter [95% CI, 565×10^3 to 5764×10^3]). Similar results were observed in the per-protocol population.

SAFETY

There were no vaccine-related serious adverse events (Table 3). Serious adverse events were of similar type and incidence in the two groups, with most attributed to injection drug use. Severe solicited adverse events in the 8 days after injection were rare (Table 3). Solicited systemic adverse events that occurred in at least 10% of participants in either group occurred in similar percentages of vaccine and placebo recipients (Table S8). The most frequent laboratory adverse event was an elevation in ALT level, a finding known to be associated with substance use[17] and with HCV infection. Other than ALT elevation, grade 3 or 4 laboratory adverse events occurred in less than 1% of participants (Table 3). Laboratory events of all grades are shown in Table S9.

IMMUNOGENICITY

Because HCV infection induces HCV-specific T-cell responses, immunogenicity was assessed before HCV infection. Immunogenicity data were available for 145 vaccine recipients (53%) and 149 placebo participants (54%). T-cell responses to HCV were detected in 78% of vaccine recipients and 3% of placebo recipients. The geometric mean ELISpot responses in each group over time are shown in Table S10. Among the placebo recipients, ELISpot responses did not change substantially over the course of the trial. The peak

interferon-γ ELISpot responses across each vaccine antigen pool among vaccine recipients are shown in Figure 1. The median of maximum interferon-γ ELISpot results summed for all pools for all vaccine recipients was 428.3 spot-forming cells per million PBMCs (range, 0 to 3443).

DISCUSSION

The data from this randomized, double-blind, placebo-controlled trial of ChAd3-NSmut and MVA-NSmut show that the vaccine regimen did not cause serious adverse events and did elicit T-cell responses against HCV proteins; however, it was not associated with a lower incidence of chronic HCV infection than placebo.

Because persons who inject drugs have the highest incidence of HCV infection, targeting this population for testing and implementing preventive vaccines is critical[18]; however, it is also challenging. Scheduling interim analyses to assess retention was important, and ongoing outreach was essential to maximize participant engagement. The trial required significant resources and expertise to engage persons who inject drugs; however, it showed the feasibility of conducting rigorous vaccine research involving this population.

Some studies have shown lower vaccine immunogenicity in persons who inject drugs.[19,20] Consistent with these observations, peak immune responses were lower in our trial than in the trials of this vaccine regimen that have involved healthy volunteers.[9] Responses in healthy volunteers may better represent vaccine immunogenicity if the vaccine is used universally as a way to prevent transmission. Nevertheless, an effective vaccine against HCV will ideally have sufficient immunogenicity to provide protection if it is administered to persons who inject drugs.

Randomization was stratified according to sex because vaccines can be less immunogenic in men and because women have higher rates of spontaneous HCV clearance.[11,21,22] Because persons who inject drugs are predominantly male and because screening failure due to anemia was more common among women, men were disproportionately enrolled in the trial, which limited our ability to examine sex-associated outcomes. Strengths of this trial include the racial and ethnic diversity of the study population and the use of placebo to provide data on background levels of adverse events related to drug use and HCV infection.

The reasons for the lack of a vaccine effect on the incidence of chronic infection are unknown. Adenoviral vectors can be less immunogenic in persons with vector cross-reactive antibodies, which may be more common in persons who inject drugs.[23,24] Alternatively, previous exposure to trace amounts of HCV that are insufficient to induce seroconversion could reduce immune responses during subsequent infection, as shown previously in nonhuman primates.[25] Finally, the vaccine did not contain HCV envelope proteins, the target of neutralizing antibodies that could reduce incident infection or enhance clearance.[26,27] Persistence in the face of vaccine-induced T-cell responses could be due to viral escape from immune pressure, as occurs in persistent natural HCV infection, or to the limited cross-reactivity of vaccine-induced T cells to infecting HCV strains.[28–30]

Studies showing that persons with HCV infection who inject drugs rarely seek HCV treatment, in spite of the safety and efficacy of current treatments, underscore the importance of vaccination to prevent infection.[31–33] In addition to other strategies for HCV infection prevention, screening, and treatment, a prophylactic HCV vaccine will be needed for successful global control of HCV infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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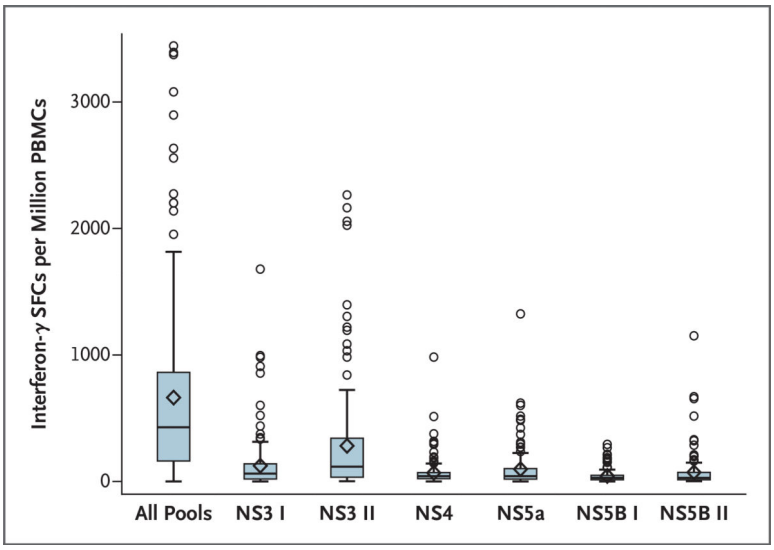

Figure 1. Peak Vaccine-Induced T-Cell Responses in the Vaccine Group.

Peak responses (at 1 week after the MVA-NSmut injection) were assessed by inteferon-γ enzyme-linked immunosorbent spot assay according to nonstructural (NS) protein pool. In the box-and-whisker plots, the horizontal line indicates the median, the top and bottom of the box the interquartile range, the diamond the mean, and the whiskers the 95% confidence interval. PBMC denotes peripheral blood mononuclear cell, and SFC spot-forming cell.

Table 1.

Baseline Characteristics of the Participants.

Characteristic	Vaccine Group (N = 275)*	Placebo Group (N = 273)*	All Participants (N = 548)
Age — yr			
Median	30.0	29.0	29.0
Range	18–45	18–45	18–45
Sex — %			
Female	22	23	22
Male	78	77	78
Body-mass index†			
Median	24.4	24.3	24.3
Range	17.2–55.5	16.8–53.4	16.8–55.5
Hispanic ethnic group — %‡	15	14	14
Race or ethnic group — %‡			
American Indian or Alaska Native	3	<1	2
Asian, Native Hawaiian, or Pacific Islander	1	1	1
Black or African American	23	19	21
White	58	64	61
Multiracial	12	11	11
Not reported	3	4	4
IFNL3 CC genotype — %§	41	41	41

*One participant who had been randomly assigned to the placebo group was erroneously given vaccine for both doses and is classified within the vaccine group in all summaries and analyses.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡Race and ethnic group were reported by the participants.

§The *IFNL3* CC genotype, which has been shown to enhance resolution of hepatitis C virus (HCV) infection,[12] was determined from the rs12979860 single-nucleotide polymorphism.

Table 2.

Vaccine Efficacy against Chronic HCV Infection at 6 Months.*

Analysis and Population†	Vaccine (N = 275)		Placebo (N =273)		Vaccine Efficacy (95% CI)‡	Hazard Ratio (95% CI)§	P Value¶
	Censored Data	Chronic Infection	Censored Data	Chronic Infection			
	number of participants				*percent*		
Primary efficacy analysis, per-protocol population‖	261	14	259	14	−53 (−255 to 34)	1.53 (0.66–3.55)	0.31
Secondary efficacy analysis, modified intention-to-treat population	256	19	257	17	−66 (−250 to 21)	1.66 (0.79–3.50)	0.18

*Included in the table are participants who received the assigned injections plus the two participants (one in each group) who received no injections. Participants' data were included at the point at which the protocol definition of chronic infection was met or were censored at the point at which at least one of the analysis population criteria was no longer met, whichever came first.

†The modified intention-to-treat population included all participants who received the first injection, were HCV negative at the time of the first injection, and had sufficient follow-up data (at least three clinic visits after the second injection). The per-protocol population included participants who met the criteria for the modified intention-to-treat population, received both injections, and had no major protocol deviations that would compromise the assessment of vaccine efficacy.

‡Vaccine efficacy was calculated as 100 × (1 − hazard ratio).

§Hazard ratios and 95% confidence intervals were obtained from a stratified Cox regression.

¶P values are from a score test comparing the groups, obtained from stratified Cox regression.

‖In the per-protocol analysis, 202 vaccine recipients and 199 placebo recipients were eligible for the 6-month analysis throughout their follow-up or until their visit 6 months after infection, whichever came first. In total, 73 of 275 vaccine recipients and 74 of 273 placebo recipients were excluded because they met one or more exclusion criteria before that time point (Table S5).

Table 3.

Safety End Points.*

Event	Participants with an Event after Dose 1		Participants with an Event after Dose 2		Participants with an Eventafter Either Dose	
	no./total no.	*% (95% CI)*	*no./total no.*	*% (95% CI)*	*no./total no.*	*% (95% CI)*
Vaccine- or placebo-related serious adverse event						
Vaccine	0/274	0 (0–1)	0/228	0 (0–2)	0/274	0 (0–1)
Placebo	0/272	0 (0–1)	0/227	0 (0–2)	0/272	0 (0–1)
Severe solicited local adverse event†‡						
Vaccine	0/274	0 (0–1)	1/228	<1 (0–2)	1/274	<1 (0–2)
Placebo	0/272	0 (0–1)	0/227	0 (0–2)	0/272	0 (0–1)
Severe solicited systemic adverse event†§						
Vaccine	0/274	0 (0–1)	1/228	<1 (0–2)	1/274	<1 (0–2)
Placebo	0/272	0 (0–1)	0/227	0 (0–2)	0/272	0 (0–1)
Any laboratory adverse event						
Vaccine	70/258	27 (22–33)	73/220	33 (27–40)	102/262	39 (33–45)
Placebo	48/259	19 (14–24)	49/224	22 (17–28)	76/261	29 (24–35)
Grade 3 or 4 laboratory adverse events						
Increase in ALT level¶						
HCV infected						
Vaccine	1/4	25 (1–75)	4/8	50 (19–81)	4/8	50 (19–81)
Placebo	0/5	0 (50–100)	3/9	33 (10–68)	3/10	30 (9–62)
HCV uninfected						
Vaccine	1/258	<1 (0–2)	0/213	0 (0–2)	1/262	<1 (0–2)
Placebo	0/258	0 (0–1)	0/217	<1 (0–2)	1/260	<1 (0–2)
Increase in creatinine level						
Vaccine	0/258	0 (0–1)	0/220	0 (0–2)	0/262	0 (0–1)
Placebo	0/259	0 (0–1)	0/224	0 (0–2)	0/261	0 (0–1)
Decrease in hemoglobin level						
Vaccine	0/258	0 (0–1)	0/220	0 (0–2)	0/262	0 (0–1)
Placebo	0/259	0 (0–1)	0/224	0 (0–2)	0/261	0 (0–1)
Increase in white-cell count						

Event	Participants with an Event after Dose 1		Participants with an Event after Dose 2		Participants with an Eventafter Either Dose	
	no./total no.	*% (95% CI)*	*no./total no.*	*% (95% CI)*	*no./total no.*	*% (95% CI)*
Vaccine	0/258	0 (0–1)	0/220	0 (0–2)	0/262	0 (0–1)
Placebo	0/259	0 (0–1)	0/224	0 (0–2)	0/261	0 (0–1)
Decrease in platelet count						
Vaccine	1/258	<1 (0–2)	0/220	0 (0–2)	1/262	<1 (0–2)
Placebo	0/259	0 (0–1)	0/224	0 (0–2)	0/261	0 (0–1)

[*] The denominator for percentages was the number of participants who received at least one dose in each group for each dose number. Confidence intervals are 95% Blaker confidence intervals.

[†] Severe adverse events are classified as grade 3 or higher.

[‡] Severe induration was reported in one participant, on day 2 after MVA-NSmut injection; the severity was reported as mild on days 3 and 4, and the induration resolved on day 5.

[§] Severe headache was reported in one participant, on day 0 after MVA-NSmut injection; the severity was reported as severe on day 1, and the headache resolved on day 2.

[¶] Adverse events related to alanine aminotransferase (ALT) levels were analyzed separately among HCV-infected participants and HCV-uninfected participants because increases in ALT levels are characteristic of HCV infection. An increase in ALT level within 30 to 37 days after receipt of vaccine or placebo in the HCV-infected group was attributed to HCV infection. Data in the rows for infected participants correspond to samples collected after a confirmed HCV infection. Data in the rows for uninfected participants correspond to samples collected before any confirmed HCV infection. Participants may be included in both infected and uninfected rows.