# Safety and immunogenicity of a novel recombinant adenovirus type-5 vector-based Ebola vaccine in healthy adults in China: preliminary report of a randomised, double-blind, placebo-controlled, phase 1 trial

*Feng-Cai Zhu, Li-Hua Hou, Jing-Xin Li, Shi-Po Wu, Pei Liu, Gui-Rong Zhang, Yue-Mei Hu, Fan-Yue Meng, Jun-Jie Xu, Rong Tang, Jin-Long Zhang, Wen-Juan Wang, Lei Duan, Kai Chu, Qi Liang, Jia-Lei Hu, Li Luo, Tao Zhu, Jun-Zhi Wang, Wei Chen*

*Lancet* 2015; 385: 2272–79

Published Online March 25, 2015 http://dx.doi.org/10.1016/S0140-6736(15)60553-0

See Comment page 2229

**Jiangsu Provincial Center for Disease Control and Prevention, Nanjing, Jiangsu Province, China** (F-C Zhu MSc, J-X Li MSc, Y-M Hu BSc, F-Y Meng MSc, R Tang MSc, W-J Wang MSc, K Chu MSc, Q Liang MSc, J-L Hu MSc); **Beijing Institute of Biotechnology, Beijing, China** (L-H Hou PhD, S-P Wu PhD, J-J Xu PhD, J-L Zhang PhD, W Chen PhD); **Beijing Institute for Drug and Instrument Quality Control, Beijing, China** (G-R Zhang PhD); **Tianjin CanSino Biotechnology Inc, Tianjin, China** (L Duan MSc, T Zhu PhD); **Department of Public Health, Southeast University, Nanjing, Jiangsu Province, China** (Prof P Liu PhD, L Luo MSc); **and National Institute for Food and Drug Control, Beijing, China** (J-Z Wang PhD)

Correspondence to: Dr Wei Chen, Beijing Institute of Biotechnology, Fengtai District, Beijing 100071, China **cw0226@foxmail.com**

## Summary

**Background** **Up to now, all tested Ebola virus vaccines have been based on the virus strain from the Zaire outbreak in 1976. We aimed to assess the safety and immunogenicity of a novel recombinant adenovirus type-5 vector-based Ebola vaccine expressing the glycoprotein of the 2014 epidemic strain.**

**Methods** **We did this randomised, double-blind, placebo-controlled, phase 1 clinical trial at one site in Taizhou County, Jiangsu Province, China. Healthy adults (aged 18–60 years) were sequentially enrolled and randomly assigned (2:1), by computer-generated block randomisation (block size of six), to receive placebo, low-dose adenovirus type-5 vector-based Ebola vaccine, or high-dose vaccine. Randomisation was pre-stratified by dose group. All participants, investigators, and laboratory staff were masked to treatment allocation. The primary safety endpoint was occurrence of solicited adverse reactions within 7 days of vaccination. The primary immunogenicity endpoints were glycoprotein-specific antibody titres and T-cell responses at day 28 after the vaccination. Analysis was by intention to treat. The study is registered with ClinicalTrials.gov, number NCT02326194.**

**Findings** **Between Dec 28, 2014, and Jan 9, 2015, 120 participants were enrolled and randomly assigned to receive placebo (n=40), low-dose vaccine (n=40), or high-dose vaccine. Participants were followed up for 28 days. Overall, 82 (68%) participants reported at least one solicited adverse reaction within 7 days of vaccination (n=19 in the placebo group *vs* n=27 in the low-dose group *vs* n=36 in the high-dose group; p=0·0002). The most common reaction was mild pain at the injection site, which was reported in eight (20%) participants in the placebo group, 14 (35%) participants in the low-dose group, and 29 (73%) participants in the high-dose vaccine group (p<0·0001). We recorded no statistical differences in other adverse reactions and laboratory tests across groups. Glycoprotein-specific antibody titres were significantly increased in participants in the low-dose and high-dose vaccine groups at both day 14 (geometric mean titre 421·4 [95% CI 249·7–711·3] and 820·5 [598·9–1124·0], respectively; p<0·0001) and day 28 (682·7 [424·3–1098·5] and 1305·7 [970·1–1757·2], respectively; p<0·0001). T-cell responses peaked at day 14 at a median of 465·0 spot-forming cells (IQR 180·0–1202·5) in participants in the low-dose group and 765·0 cells (400·0–1460·0) in those in the high-dose group. 21 (18%) participants had mild fever (n=9 in the placebo group, n=6 in the low-dose group, and n=6 in the high-dose group). No serious adverse events were recorded.**

**Interpretation** **Our findings show that the high-dose vaccine is safe and robustly immunogenic. One shot of the high-dose vaccine could mount glycoprotein-specific humoral and T-cell response against Ebola virus in 14 days.**

**Funding** **China National Science and Technology, Beijing Institute of Biotechnology, and Tianjin CanSino Biotechnology.**

## Introduction

The 2014 epidemic of Ebola virus in west Africa has been the largest in history since the virus was first discovered in 1976.[1,2] The virus was widely transmitted in Guinea, Liberia, and Sierra Leone, with a few cases in other countries in west Africa.[3] As of Feb 20, 2015, 23 406 suspected, probable, and laboratory-confirmed cases of Ebola virus disease were reported, causing 9457 deaths.[4] So far, no licensed vaccine against Ebola virus is available.[5]

Ebola viruses are enveloped, non-segmented, negative-strand RNA viruses belonging to the family of Filoviridae.[6,7] Five different species of Ebola virus have been identified: Zaire, Sudan, Côte d'Ivoire, Reston, and Bundibugyo. Although the newly discovered Guinea variant (Ebola virus/H sapiens-wt/GIN/2014/Makona-C15) causing the 2014 outbreak in west Africa belongs to the Zaire species,[8] it is a new variant with only 97·6% identity to the aminoacid sequence of the envelope glycoprotein of the 1976 Zaire strain.[3] As an emergency response to the largest Ebola disease epidemic, several countries accelerated the process of vaccine development and assessment; however, all vaccines are developed based on the 1976 Zaire strain.[9,10]

We assessed the safety and immunogenicity of a novel recombinant adenovirus type-5 vector-based Ebola vaccine—the first Ebola vaccine based on the 2014 Zaire Guinea epidemic strain.

## Research in context

### Evidence before this study

We searched PubMed for clinical trial reports with the terms "Ebola" or "Ebolavirus", and "vaccine", and ClinicalTrials.gov for unpublished randomised trials with no date or language restrictions, up to Feb 27, 2015. Four previous phase 1 clinical trials have been reported with a recombinant adenovirus type-5 Ebola vaccine, a bivalent DNA vaccine, a multivalent recombinant chimpanzee adenovirus type-3 vectored Ebola vaccine, and a monovalent chimpanzee adenovirus Ebola vaccine. Data from these trials showed that the Ebola glycoprotein is safe and immunogenic, and viral vectored Ebola vaccine could induce specific antibody and T-cell responses in 28 days. However, all the tested Ebola vaccines were developed based on the 1976 Zaire strain. Another 14 phase 1 clinical trials and a phase 2 clinical trial of Ebola vaccines are ongoing.

### Added value of this study

We tested a novel replication-defective adenovirus type-5 vector-based Ebola vaccine developed based on the 2014 Zaire Guinea Ebola strain, which is responsible for the present Ebola disease epidemic in west Africa. The lyophilised formulation of adenovirus type-5 Ebola vaccine is more stable and easier to store and transport than are the aqueous buffer solutions of previous vaccines. We showed that a high dose of the adenovirus type-5 vaccine with $1{\cdot}6 \times 10^{11}$ viral particles could overcome the negative effects of pre-existing adenovirus type-5 immunity and induced good Ebola glycoprotein-specific antibody and T-cell responses in participants in 14 days.

### Implications of all the available evidence

High-dose viral vectored Ebola vaccine could elicit a specific immune response against Ebola virus in 14 days, making it a potential candidate for emergency vaccination of acute protective response.

## Method

### Study design and participants

We did this randomised, double-blind, placebo-controlled, phase 1 clinical trial at one site in Taizhou County, Jiangsu Province, China. Eligible participants were adults (aged 18–60 years) who had no HIV infection and were healthy, with no hepatorenal dysfunction, as confirmed by physical examination and laboratory tests at the time of screening. Exclusion criteria were a history of seizure or mental disease, allergy to any component of the vaccine formulation, acute febrile disease on the day of enrolment, receipt of any blood products in the past 4 months, receipt of any research drugs or vaccine in the past month, and non-compliance with the study schedule. The protocol outlines further details of the inclusion and exclusion criteria.

The protocol and informed consent documents were approved by the Institutional Review Board of the Jiangsu Provincial Center of Disease Control and Prevention. All participants provided written informed consent. This study was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

### Randomisation and masking

Participants were sequentially enrolled, in a two-step manner, to receive the low-dose vaccine or placebo (group 1) or the high-dose vaccine or placebo (group 2), then randomly assigned (2:1), by computer-generated block randomisation (block size of six), to receive placebo, the low-dose vaccine, or the high-dose vaccine. Randomisation was pre-stratified by dose group—ie, group 1 or group 2. Both the vaccine and placebo were vialled and had identical packaging with a labelled randomisation code as the only identifier. Each eligible participant was assigned a sequential number according to their sequence of enrolment and then received vaccine or placebo labelled with the same number. After the study was unmasked, we pooled half the placebo recipients from group 1 and half from group 2 and analysed them as one treatment group. Individuals involved in the randomisation and masking process did not participate in any other process of the study. All participants, investigators, and laboratory staff were masked to treatment allocation.

### Procedures

The present experimental vaccine, developed by Beijing Institute of Biotechnology (Beijing, China) and Tianjin CanSino Biotechnology (Tianjin, China) is a replication-defective adenovirus type-5 vector-based vaccine expressing the glycoprotein of the 2014 Zaire Ebola virus. We used an E1-deleted and E3-deleted adenovirus type-5 vector and constructed the vaccine with the Admax system (Microbix Biosystem, ON, Canada). Vaccines were manufactured as lyophilised white powder containing $4{\cdot}0{\times}10^{10}$ adenovirus type-5 viral particles per vial, whereas the placebo contained the vaccine excipients only, with no viral particles. Viral particles in the Ebola vaccine were measured by the National Institute for Food and Drug Control (Beijing, China) with high-pressure liquid chromatography.[11]

Participants in group 1 received one shot intramuscularly in the arm with either one vial of the vaccine ($4{\cdot}0{\times}10^{10}$ viral particles) or with placebo dissolved in 1 mL sterile water for injection. High doses of the vaccine were achieved by dissolving four vials of vaccine in 1 mL×2 sterile water for injection. Participants in group 2 received either a double-shot regimen of the vaccine (a total of $1{\cdot}6{\times}10^{11}$ viral particles) or placebo, with one shot in each arm.

For the **full protocol** see http://jscdc.cn/jgzn/zzjg/kyjyk/wjtz/201503/t20150314_45160.html