Ebola vaccine development: Systematic review of pre-clinical and clinical studies, and meta-analysis of determinants of antibody response variability after vaccination

Lise Gross, Édouard Lhomme, Chloé Pasin, Laura Richert, Rodolphe Thiébaut

International Journal of Infectious Diseases 74 (2018) 83–96

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Ebola vaccine development: Systematic review of pre-clinical and clinical studies, and meta-analysis of determinants of antibody response variability after vaccination

Lise Gross[b,c], Edouard Lhomme[a,b,c,d], Chloé Pasin[a,b,c], Laura Richert[a,b,c,d], Rodolphe Thiebaut[a,b,c,d,*]

[a] INSERM, Bordeaux Population Health Research Centre, UMR 1219, Univ. Bordeaux, ISPED, F-33000, Bordeaux, France
[b] SISTM Team (Statistics in System Biology and Translational Medicine), INRIA Research Centre, Bordeaux, F-33000, France
[c] Vaccine Research Institute (VRI), Créteil, F-94000, France
[d] Pôle de Santé Publique, CHU de Bordeaux, Bordeaux, F-33000, France

ARTICLE INFO

Article history:
Received 10 April 2018
Received in revised form 20 June 2018
Accepted 28 June 2018
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Ebola
Vaccine
Review
Meta-analysis
Humans
Nonhuman primates

ABSTRACT

Objectives: For Ebola vaccine development, antibody response is a major endpoint although its determinants are not well known. We aimed to review Ebola vaccine studies and to assess factors associated with antibody response variability in humans.
Methods: We searched PubMed and Scopus for preventive Ebola vaccine studies in humans or non-human primates (NHP), published up to February 2018. For each vaccination group with Ebola Zaire antibody titre measurements after vaccination, data about antibody response and its potential determinants were extracted. A random-effects meta-regression was conducted including human groups with at least 8 individuals.
Results: We reviewed 49 studies (202 vaccination groups including 74 human groups) with various vaccine platforms and antigen inserts. Mean antibody titre was slightly higher in NHP (3.10, 95% confidence interval [293; 327]) than in humans (2.75 [257; 293]). Vaccine platform ($p < 0{\cdot}001$) and viral strain used for antibody detection ($p < 0{\cdot}001$) were associated with antibody response in humans, but adjusted heterogeneity remained at 95%.
Conclusions: Various platforms have been evaluated in humans, including Ad26, Ad5, ChimpAd3, DNA, MVA, and VSV. In addition to platforms, viral strain used for antibody detection influences antibody response. However, variability remained mostly unexplained. Therefore, comparison of vaccine immunogenicity needs randomised controlled trials.

Introduction

Following the deadly 2013-2016 epidemic in West Africa, there has been an accelerated development of several candidates for an Ebola preventive vaccine. Outbreaks of Ebola virus disease (EVD) have occurred recurrently and unpredictably for the past 40 years with a high lethality rate (Liu et al., 2015). The 2013-2015 outbreak was unprecedented in scale, with over 28,000 cases and more than 11,000 deaths (Ebola Situation Report, 2016). Incidental cases are still reported as recently in the Democratic Republic of Congo in May 2017 (Dhama et al., 2015). In the absence of any specific treatment, EVD prevention and control measures are primarily based on case identification and isolation, early non-specific medical care, surveillance of suspect cases, and safe burial practices (Henao-Restrepo et al., 2017). These measures are now sometimes complemented by ring vaccination of contacts of cases, based on the promising results of a phase III cluster-randomized ring vaccination efficacy trial conducted in Guinea in 2015 (Ohimain, 2016). However, the vaccine used for ring vaccination (rVSV ZEBOV vaccine) is not yet licenced and conducting new efficacy trials for licencing is not feasible in the absence of a large outbreak. Nevertheless, preparation for future outbreaks is required and the licensing of one or several preventive vaccines for stockpiling is a priority.

Several candidate vaccines strategies have been investigated since the first reported EVD outbreak in 1976. During and following

* Corresponding author at: INSERM U1219, INRIA SISTM, ISPED, Bordeaux University, 146 Rue Leo Saignat, 33076, Bordeaux Cedex, France.
E-mail address: Rodolphe.Thiebaut@u-bordeaux.fr (R. Thiebaut).

https://doi.org/10.1016/j.ijid.2018.06.022

the 2013-2015 epidemic, the process of vaccine development has been substantially accelerated, and several strategies have been moved into clinical phases. Despite the promising results of the ring vaccination trial in Guinea (Ohimain, 2016), many questions, such as durability of immune responses, and immune responses and protection in specific sub-groups such as young children, remain to be addressed and Ebola vaccine development continues to be very active. Based on their delivery technologies, several candidate vaccine platforms can be distinguished: whole-virus vaccines, DNA vaccines, virus-like particles vaccines, and recombinant vaccines with different viral vectors (vesicular stomatitis virus or VSV, modified vaccinia Ankara or MVA, human adenovirus or Ad, and chimpanzee adenovirus or ChAd) (World Health Organisation, 2013). Each platform may use specific dose levels and Ebola antigen inserts.

Vaccine trials aim to assess vaccine safety and immunogenicity in phase I and II trials in humans prior to testing for a protective effect in phase III. Assessment of vaccine efficacy during pre-clinical and clinical studies is required to go through the vaccine license steps. Clinical protection from EVD in human populations is impossible to observe outside an epidemic period. In the non-epidemic context, Ebola vaccines are thus currently evaluated by using a main immunogenicity endpoint: the antibody response after vaccination. There is no definite evidence that antibody response is the correlate of protection or surrogate endpoint for efficacy in humans, that is a specific immune response to vaccine associated with vaccine-induced protection (Sullivan et al., 2009) and it may vary according to the vaccine platforms (Sullivan et al., 2000a,b). However, we know that antibody response is correlated with survival after challenge in nonhuman primate models, which is the nearest model to humans for EVD and hence the animal gold standard to test candidate Ebola vaccines; this association is found consistently for different Ebola candidate vaccines (Wong et al., 2012; Food and Drug Administration, 2015; Sridhar, 2015).

For these reasons, antibody response is used as the main criterion to assess the Ebola candidate vaccines in phase I/II trials. In the absence of the possibility to conduct additional phase III trials, regulatory pathways not requiring such efficacy results are also under discussion (Food and Drug Administration, 2015). Significant variations in antibody responses are observable across studies, which could be due to the different types of vaccines evaluated, or not. Various factors are suspected to influence the level of antibody response beyond the vaccine features (vaccine platform, Ebola viral insert, dosage, single injection or boost, . . .) such as the measurement techniques (time of measurement, antigen used to detect antibody response, . . .) or the population type (human or nonhuman primates, age, sex, study site, . . .). There is a lack of quantification of the contribution of each factor in the observed variation of the reported antibody responses.

Although previous reviews exist on Ebola vaccines (Ohimain, 2016; Sridhar, 2015; Wu et al., 2015), the specific topic of antibody response determinants has not yet been addressed by a systematic review or meta-analysis. Yet, the identification of factors potentially associated with antibody response after Ebola vaccination could provide relevant information for further vaccine trials and for regulatory decision making.

By conducting this systematic review with a meta-analysis, we aimed to determine whether the reported antibody response variability in Ebola vaccine trials is not only determined by the vaccine platform but also by other characteristics of vaccine and by population and measurement characteristics and to quantify these factors.

Methods

Search strategy and selection criteria

Studies were identified by searching electronic databases PubMed and Scopus. Pubmed was searched using the following terms: (« hemorrhagic fever, ebola » [MeSH Terms] OR « ebola » [All fields] OR « ebolavirus » [MeSH Terms] OR « ebolavirus » [All fields]) AND (« vaccines » [MeSH Terms] OR « vaccines » [All fields] OR « vaccine » [All Fields]). Scopus was searched using the following terms TITLE-ABS-KEY (ebola) AND TITLE-ABS-KEY (vaccine). Additionally, the Clinicaltrials.gov website was searched to identify unpublished and ongoing studies. Several experts in the field were contacted to find papers which could be not indexed in databases. Reference lists of relevant papers and reviews were examined to identify further articles.

The search was performed on March 23, 2016 and updated as of February 24, 2018 with a publication date limit of the same date in order to identify all published studies which met the inclusion criteria and without restriction on language. All preventive Ebola vaccine clinical trials conducted in humans or in nonhuman primates and with a measure of Ebola Zaire antibody titre after vaccination were included in our systematic review. Studies were excluded in case of duplicate study, studies without original data, preclinical studies conducted in animals other than nonhuman primates or in vitro experimentation.

Data extraction

A first step of selection was performed on the title and abstract, and then a second step was performed after reading the full article. Two authors independently assessed each full article to include papers matching the review's inclusion criteria. Disagreements between reviewers were resolved by consensus.

Data were extracted by two independent reviewers, with differences reconciled by consensus. The following variables were extracted: paper identification (title, first author, publication year), study design, inclusion and exclusion criteria, characteristics of the population (number of subjects; human or nonhuman primates; proportion of women, average age and study site for clinical trials; and animal species for pre-clinical studies using nonhuman primates), characteristics of vaccine (vaccine platform in terms of delivery technology used, specific vector for recombinant vaccines, Ebola viral insert, dosage, route of administration, vaccination schedule), characteristics of measurement techniques (time interval between last injection and measure, strain and nature of antigen used to detect antibody response, measurement method), antibody response after vaccination (geometric mean titre and its variance). Regarding the antibody response after vaccination, geometric mean titre was extracted from the text or estimated from figures. If a single vaccination group had more than one measure of antibody response, data from measurement after each injection were extracted. Therefore, if available, measurement post-prime and measurement post-boost from a same vaccination group were both included in our meta-analysis. If several measurements post-prime or if several measurements post-boost were available, for each injection we extracted the one closest to 28 days after injection, which is a standard time point in Ebola vaccine trials. Variance of titre (within-group variance) was extracted directly from the text or calculated from confidence interval or from individual values. The present study was registered in PROSPERO (no. 54303).

Data analysis

For all analyses, the statistical unit used was the vaccination group (one or several groups for a single study), i.e. a protocol-defined group undergoing the same intervention and follow-up procedures (such as a randomized arm of a clinical trial or an animal group in NHP studies).

First descriptive analyses were performed among all groups, separately for nonhuman primates and for humans. Then, a random-effect meta-regression analysis was performed including only human groups with 8 individuals or more. This threshold allowed both to have sufficient inter-individual variability in each group and to avoid excluding too many groups. Thus, it was not possible to perform the regression analysis with NHP studies because of the usual small sample size of the groups. The effect of every potential determinant of antibody response was assessed through fixed effects. A random intercept was allowed to capture between-group variability not explained by the fixed effects. The residual variance (within-group variance) was fixed in the model according to the values resulting from data extraction as described by Van Houwelingen (Van Houwelingen et al., 2002).

Each potential determinant associated in unadjusted analyses with a p-value <0.25 was included in the multivariable model using forward step-wise selection. The heterogeneity was checked visually with forest plots and quantified by using the Q test. The proportion of total variation across groups due to heterogeneity (I^2) and the amount of variability explained by the factors included in the random-effect model (R^2) were estimated. Antibody titres after vaccination were log transformed in the model.

For the meta-regression analysis, the dosage variable was categorized into "low dose" or "high dose" per vaccine platform, since units of measurement for dose level were platform-dependent. For each unit of dose measurement and each vaccine platform, the average dose level among the human groups included in the meta-regression model was used as a classification threshold for this variable; if only one dose level was assessed for a vaccine platform, the dosage variable was defined as undifferentiated. The absence of interaction between vaccine platform and dosage was checked (likelihood ratio test: p = 0.223).

All analyses were performed using the metafor package of R (i386 3.2.2 version, the R Foundation, Vienna, Austria).

Results

Study selection

The selection process of the studies and vaccination groups is described in Figure 1.

The search yielded a total of 2166 studies. Of these, 49 met the inclusion criteria to the research question corresponding to 202 vaccination groups. Unpublished clinical trials and one trial found by contact with an expert were excluded since no results were available. Studies not reporting any antibody measurements were also excluded. This led to the exclusion of the "Ebola ça suffit" ring vaccination trial conducted in Guinea, the only trial that was able to assess clinical efficacy in humans so far (Ohimain et al., 2016). This trial was conducted under emergency conditions and did not collect blood samples for immunogenicity measurements.

Table 1 shows details of all trials included in the systematic review: 32 studies were conducted in NHP, 13 trials in humans were phase 1, two trials phase 1/2, and two phase 2. The number of trials has increased significantly since the last outbreak of EVD. Clinical trials were conducted mostly in Europe and North America (Figure 2).

Description of included vaccination groups

Among the 202 vaccination groups included in our systematic review, 74 were human groups and 128 were non-human primate groups. The distribution of the number of individuals by groups is

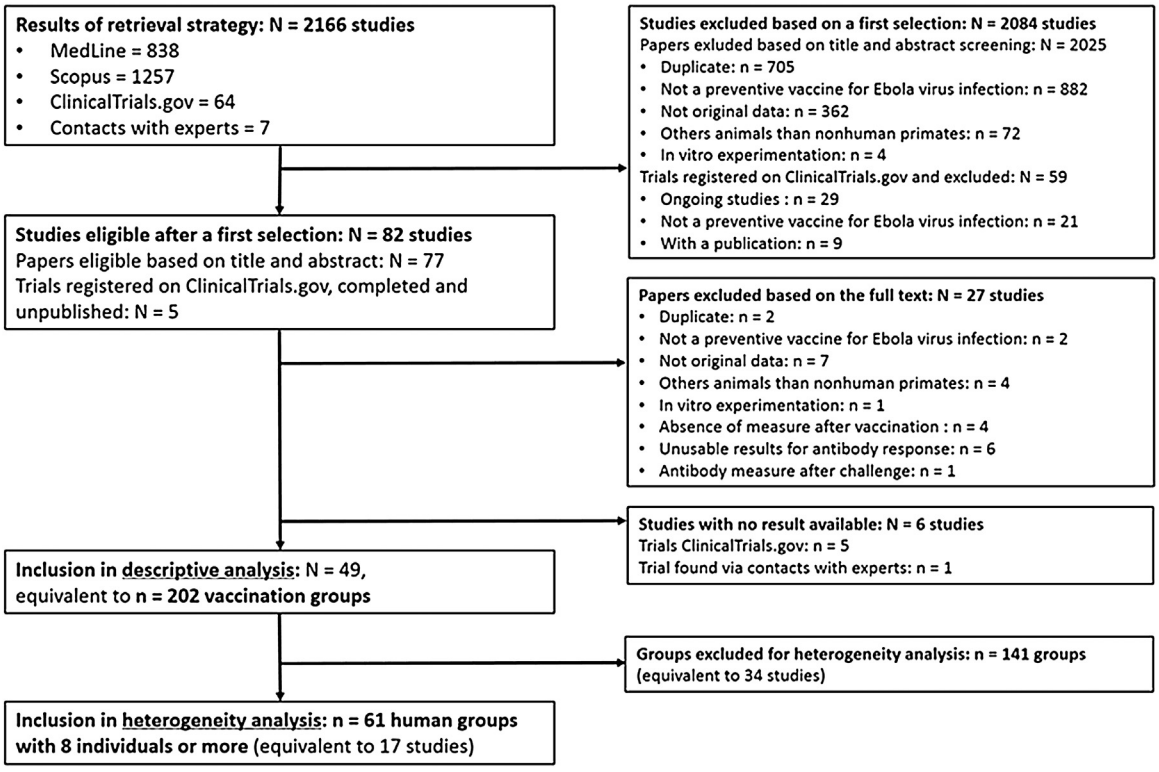

Figure 1. Flow chart for study/vaccination group selection.

Table 1
Main characteristics of the preclinical studies and clinical trials included in the systematic review.

Title	First author	Year of publication	Population and study features	Vaccine(s)	Measurement of antibody response
Phase 1 Trials of rVSV Ebola Vaccine in Africa and Europe (Agnandji et al., 2016)	Agnandji	2016	Humans (Germany, Switzerland, Gabon, Kenya), phase 1, randomization and placebo	Recombinant VSV-GP(Zaire), single injection, IM, 300 000 to 50 million PFU	Antibodies anti GP (Kikwit), D28 or D180
Successful topical respiratory tract immunization of primates against Ebola virus (Bukreyev et al., 2007)	Bukreyev	2007	NHP: rhesus monkeys; placebo	Recombinant HPIV3(+/− modified)-GP +/− NP (Zaire Mayinga), single injection +/− boost D28, IN + IT, 4 to 20 million TCID50	Antibodies anti virion, D28 (or D39 after boost)
Mucosal parainfluenza virus-vectored vaccine against Ebola virus replicates in the respiratory tract of vector-immune monkeys and is immunogenic (Bukreyev et al., 2010)	Bukreyev	2010	NHP: rhesus monkeys (+/− HPIV3 seropositive); placebo	Recombinant HPIV3-GP(Zaire Mayinga), boost D28, IN + IT, 20 million PFU	Antibodies anti virion, D28
Safety and immunogenicity of a chimpanzee adenovirus-vectored Ebola vaccine in healthy adults: a randomised, double-blind, placebo-controlled, dose-finding, phase 1/2a study (De Santis et al., 2016)	De Santis	2016	Humans (Switzerland), phase 1/2, randomization and placebo	Recombinant ChAd3-GP(Zaire Mayinga), single injection, IM, 25 to 50 billion VP	Antibodies anti GP (Mayinga), D28, results in EC90
Respiratory tract immunization of non-human primates with a Newcastle disease virus-vectored vaccine candidate against Ebola virus elicits a neutralizing antibody response (DiNapoli et al., 2010)	DiNapoli	2010	NHP: rhesus monkeys; no placebo	Recombinant NDV-GP(Zaire Mayinga) or HPIV3-GP(Zaire Mayinga), boost D28, IN + IT, 20 million PFU	Antibodies anti virion (Mayinga), D28
A Monovalent Chimpanzee Adenovirus Ebola Vaccine Boosted with MVA (Ewer et al., 2016)	Ewer	2016	Humans (United Kingdom), phase 1, no randomization, no placebo	Recombinant ChAd3-GP(Zaire Mayinga) 10 to 50 billion VP, boost between D7 and D46 with recombinant MVA-GP(Zaire Mayinga + Sudan Gulu)/NP(Taï Forest) 150 to 300 millions PFU, IM	Antibodies anti GP (Mayinga) or anti virion (Makona)
Vesicular stomatitis virus-based vaccines protect nonhuman primates against aerosol challenge with Ebola and Marburg viruses (Geisbert et al., 2008a,b)	Geisbert	2008	NHP: cynomolgus macaques; placebo	Recombinant VSV-GP(Zaire Kikwit), single injection, 20 million PFU	Antibodies anti virion (Kikwit), D14 or D27
Vesicular stomatitis virus-based ebola vaccine is well-tolerated and protects immunocompromised nonhuman primates (Geisbert et al., 2008a,b)	Geisbert	2008	NHP: rhesus monkeys (SHIV infected); placebo	Recombinant VSV-GP(Zaire Mayinga), single injection, IM, 10 million PFU	Antibodies anti virion (Mayinga), D14
Single-injection vaccine protects nonhuman primates against infection with marburg virus and three species of ebola virus (Geisbert et al., 2009)	Geisbert	2009	NHP: cynomolgus macaques and rhesus monkeys; placebo	Recombinant VSV-GP(Zaire Mayinga and/or Sudan Boniface +/− Marburg), single injection +/− boost D14, IM, 10 to 20 million PFU	Antibodies anti virion, between D14 and D28
Recombinant adenovirus serotype 26 (Ad26) and Ad35 vaccine vectors bypass immunity to Ad5 and protect nonhuman primates against ebolavirus challenge (Geisbert et al., 2011)	Geisbert	2011	NHP: cynomolgus macaques (+/− Ad5 seropositive); placebo	Recombinant Ad5, Ad26, or Ad35, or prime Ad26 + boost Ad35 D28 - GP (Zaire + Sudan Gulu), IM, 20 to 200 billion VP	Antibodies anti GP, D21, results in EC90
Codon-optimized filovirus DNA vaccines delivered by intramuscular electroporation protect cynomolgus macaques from lethal Ebola and Marburg virus challenges (Grant-Klein et al., 2015)	Grant-Klein	2015	NHP: cynomolgus macaques; placebo	Vaccin ADN-GP(Zaire +/− Sudan, Reston et Marburg), 3 injections (28 jours apart), electroporation IM, 500 μg to 2 mg	Antibodies anti GP (Mayinga) ΔTM or ΔMuc, D28
Demonstration of cross-protective vaccine immunity against an emerging pathogenic Ebolavirus Species (Hensley et al., 2010)	Hensley	2010	NHP: cynomolgus macaques; placebo	Vaccin ADN-GP(Zaire Mayinga + Sudan Gulu), 4 injections IM, 4 mg (28 to 42 days apart +/− boost D371 recombinant Ad5-GP (Zaire Mayinga) IM 100 billion VP	Antibodies anti GP, D21 or D371, results in EC90
Venezuelan equine encephalitis virus replicon particle vaccine protects nonhuman primates from intramuscular and aerosol challenge with ebolavirus (Herbert et al., 2013)	Herbert	2013	NHP: cynomolgus macaques; placebo	VRP GP(Zaire Kikwit +/− Sudan Boniface), single injection, IM, 10 to 20 billion FFU	Antibodies anti GP, D28
The effect of dose on the safety and immunogenicity of the VSV Ebola candidate vaccine: a randomised double-blind, placebo-controlled phase 1/2 trial (Huttner et al., 2015)	Huttner	2015	Humans (Switzerland), phase 1/2, randomization and placebo	Recombinant VSV-GP(Zaire), single injection, IM, 300 000 PFU	Antibodies anti GP, D28
Live attenuated recombinant vaccine protects nonhuman primates against Ebola and Marburg viruses (Jones et al., 2005)	Jones	2005	NHP: cynomolgus macaques; placebo	Recombinant VSV-GP(Zaire Mayinga), single injection, IM, 10 million PFU	Antibodies anti virion, D28
Phase 2 Placebo-Controlled Trial of Two Vaccines to Prevent Ebola in Liberia (Kennedy et al., 2017)	Kennedy	2017	Humans (Liberia), phase 2, randomization and placebo	Recombinant ChAd3-GP(Saire) 100 billion VP or VSV-GP(Zaire Kikwit) 20 million PFU, single injection, IM	Antibodies anti GP (Kikwit), D28
Safety and immunogenicity of Ebola virus and Marburg virus glycoprotein DNA vaccines assessed separately and concomitantly in healthy Ugandan adults: a phase 1b,	Kibuuka	2015	Humans (Uganda), phase 1b; randomization and placebo	Vaccin ADN GP(Zaire + Sudan +/− Marburg), 3 injections, IM, 4 mg	Antibodies anti GP, D28

Table 1 (*Continued*)

Title	First author	Year of publication	Population and study features	Vaccine(s)	Measurement of antibody response
randomised, double-blind, placebo-controlled clinical trial (Kibuuka et al., 2015)					
A replication defective recombinant Ad5 vaccine expressing Ebola virus GP is safe and immunogenic in healthy adults (Ledgerwood et al., 2010)	Ledgerwood	2010	Humans (USA), phase 1; randomization and placebo	Recombinant Ad5-GP(Zaire Mayinga + Sudan Gulu), single injection, IM, 2 to 20 billion VP	Antibodies anti GP (Mayinga), D28
Chimpanzee Adenovirus Vector Ebola Vaccine – Preliminary Report (Ledgerwood et al., 2015)	Ledgerwood	2015	Humans (USA), phase 1, no randomization and no placebo	Recombinant ChAd3-GP(Zaire Mayinga + Sudan), single injection, IM, 20 or 200 billion VP	Antibodies anti GP (Mayinga or Zaire-Guinea), D28, results in EC90
Immunity duration of a recombinant adenovirus type-5 vector-based Ebola vaccine and a homologous prime-boost immunisation in healthy adults in China: final report of a randomised, double-blind, placebo-controlled, phase 1 trial (Li et al., 2017)	Li	2017	Humans (China), phase 1; randomization and placebo	Recombinant Ad5-GP(Zaire Makona), 2 injections (168 days apart), IM, 40 or 160 billion VP	Antibodies anti GP, D28, results in EC90
A DNA vaccine for Ebola virus is safe and immunogenic in a phase I clinical trial (Martin et al., 2006)	Martin	2006	Humans (USA), phase 1, randomization and placebo	Vaccin ADN GP/NP(Zaire Mayinga) + GP (Sudan Gulu), 3 injections (28 days apart), IM, 2 to 8 mg	Antibodies anti GP or NP (Mayinga), D28
Antibodies are necessary for rVSV/ZEBOV-GP-mediated protection against lethal Ebola virus challenge in nonhuman primates (Marzi et al., 2013)	Marzi	2013	NHP: cynomolgus macaques (with depletion CD4+ or CD8 + or CD20+); placebo	Recombinant VSV-GP(Zaire Mayinga), single injection, IM, 10 million PFU	Antibodies anti GP, D28
Vesicular stomatitis virus-based vaccines against Lassa and Ebola viruses (Marzi et al., 2015a,b,c)	Marzi	2015	NHP: cynomolgus macaques (vaccinated with VSV-Lassa); placebo	Recombinant VSV-GP(Zaire Mayinga), single injection, IM, 10 million PFU	Antibodies anti GP, day of measurement non specified
Vaccines. An Ebola whole-virus vaccine is protective in nonhuman primates (Marzi et al., 2015a,b,c)	Marzi	2015	NHP: cynomolgus macaques; placebo	Attenuated whole-virus Zaire Mayinga, single injection, IM, 10 to 20 million FFU	Antibodies anti GP, D28
EBOLA VACCINE. VSV-EBOV rapidly protects macaques against infection with the 2014/15 Ebola virus outbreak strain (Marzi et al., 2015a,b,c)	Marzi	2015	NHP: cynomolgus macaques; placebo	Recombinant VSV-GP(Zaire Kikwit), single injection, unique, 50 million PFU	Antibodies anti GP, between D3 and D28
Cytomegalovirus-based vaccine expressing Ebola virus glycoprotein protects nonhuman primates from Ebola virus infection (Marzi et al., 2016)	Marzi	2016	NHP: rhesus monkeys (CMV seropositive); placebo	Recombinant RhCMV-GP(Zaire Mayinga), boost D84, SC, 10 million PFU	Antibodies anti GP, D28
Vaccination With a Highly Attenuated Recombinant Vesicular Stomatitis Virus Vector Protects Against Challenge With a Lethal Dose of Ebola Virus (Matassov et al., 2015)	Matassov	2015	NHP: rhesus monkeys; placebo	Recombinant VSV-GP(Zaire Mayinga), single injection, IM, 10 million PFU	Antibodies anti GP, D21
Aerosolized Ebola vaccine protects primates and elicits lung-resident T cell responses (Meyer et al., 2015)	Meyer	2015	NHP: rhesus monkeys; placebo	Recombinant HPIV3-GP(Zaire Mayinga) 40 to 400 million PFU or VRP(Zaire Mayinga) 10 billion PFU, boost D28, IM or aerosol or IN + IT	Antibodies anti virion (Mayinga), D23 or D28
Safety and immunogenicity of novel adenovirus type 26–and modified vaccinia ankara–vectored ebola vaccines: A randomized clinical trial (Milligan et al., 2016)	Milligan	2016	Humans (United Kingdom), phase 1, randomization and placebo	Recombinant Ad26-GP(Zaire Mayinga) 50 billion VP or recombinant MVA-GP(Zaire Mayinga + Sudan Gulu)/NP(Taï Forest) 100 millions TCID50, boost between D15 and D56, IM	Antibodies anti GP Kikwit), D28 after prime and D21 after boost
Vesicular stomatitis virus-based vaccines protect nonhuman primates against Bundibugyo ebolavirus (Mire et al., 2013)	Mire	2013	NHP: cynomolgus macaques; placebo	Recombinant VSV-GP(Zaire Mayinga and/or Sudan Boniface or Bundibugyo) +/− boost VSV-GP(Zaire Mayinga) D14, IM, 20 million PFU	Antibodies anti GP, between D22 and D29
Single-dose attenuated Vesiculovax vaccines protect primates against Ebola Makona virus (Mire et al., 2015)	Mire	2015	NHP: cynomolgus macaques; placebo	Recombinant VSV-GP(Zaire Mayinga), single injection, IM, 20 million PFU	Antibodies anti GP, D28
Protection of nonhuman primates against two species of Ebola virus infection with a single complex adenovirus vector (Pratt et al., 2010)	Pratt	2010	NHP: cynomolgus macaques or rhesus monkeys (+/− Ad5 seropositive); placebo	Recombinant CAdVax-GP(Zaire Kikwit + Sudan Boniface +/− Marburg), boost between D65 and D238, IM, 100 million to 20 billion PFU	Antibodies anti virion, between D7 and D49
A Kunjin Replicon Virus-like Particle Vaccine Provides Protection Against Ebola Virus Infection in Nonhuman Primates (Pyankov et al., 2015)	Pyankov	2015	NHP: African green monkeys; placebo	Recombinant VLP Kunjin-GP(Zaire Mayinga), boost D28, SC, 1 billion VLP	Antibodies anti virion, D21 or D28
A Monovalent Chimpanzee Adenovirus Ebola Vaccine - Preliminary Report (Rampling et al., 2015)	Rampling	2015	Humans (United Kingdom), phase 1, no randomization, no placebo	Recombinant ChAd3-GP(Zaire), single injection, IM, 10 to 50 billions VP	Antibodies anti GP, D28, results in EC90
A Recombinant Vesicular Stomatitis Virus Ebola Vaccine - Preliminary Report (Regules et al., 2015)	Regules	2015	Humans (USA), phase 1, randomization and placebo	Recombinant VSV-GP(Zaire Kikwit), single injection, IM, 3 to 20 million PFU	Antibodies anti GP (Kikwit or Mayinga), D28

Table 1 (*Continued*)

Title	First author	Year of publication	Population and study features	Vaccine(s)	Measurement of antibody response
Safety and immunogenicity of DNA vaccines encoding Ebolavirus and Marburgvirus wild-type glycoproteins in a phase I clinical trial (Sarwar et al., 2015)	Sarwar	2015	Humans (USA), phase 1, no randomization and no placebo	Vaccin ADN GP(Zaire + Sudan), 3 injections (28 days apart) + boost D168, IM, 4 mg	Antibodies anti GP, D28
Chimpanzee adenovirus vaccine generates acute and durable protective immunity against ebolavirus challenge (Stanley et al., 2014)	Stanley	2014	NHP: cynomolgus macaques; placebo	Recombinant ChAd3-GP(Zaire + Sudan), 1 to 10 billion VP or recombinant ChAd3-GP (Zaire + Sudan) or recombinant MVA-GP (Zaire + Sudan) 100 million VP, single injection, IM	Antibodies anti GP, D21, results in EC90
Development of a preventive vaccine for Ebola virus infection in primates (Sullivan et al., 2000a,b)	Sullivan	2000	NHP: cynomolgus macaques; placebo	DNA vaccine GP/NP(Zaire) + GP(Sudan + Taï Forest), 3 injections, 4 mg (28 days apart), boost D84 recombinant Ad5-GP(Z) 10 billion PFU, IM	Nature of viral antigen non specified, D28
Accelerated vaccination for Ebola virus haemorrhagic fever in non-human primates (Sullivan et al., 2003)	Sullivan	2003	NHP: cynomolgus macaques; placebo	Recombinant Ad5-GP/NP(Zaire) +/− boost D63, IM, 2000 billion VP	Antibodies anti virion, between D7 and D63
CD8+ cellular immunity mediates rAd5 vaccine protection against Ebola virus infection of nonhuman primates (Sullivan et al., 2011)	Sullivan	2011	NHP: cynomolgus macaques; placebo	Recombinant Ad5-GP(Zaire), single injection, IM, 10 billion VP	Antibodies anti GP, day of measurement non specified, results in EC90
Vaccine to confer to nonhuman primates complete protection against multistrain Ebola and Marburg virus infections (Swenson et al., 2008)	Swenson	2008	NHP: cynomolgus macaques; placebo	Recombinant Ad5-GP/NP(Zaire) + GP(Sudan Boniface), boost D63, IM, 40 billion PFU	Antibodies anti virion, D14 after prime and D21 after boost
Use of ChAd3-EBO-Z Ebola virus vaccine in Malian and US adults, and boosting of Malian adults with MVA-BN-Filo: a phase 1, single-blind, randomised trial, a phase 1b, open-label and double-blind, dose-escalation trial, and a nested, randomised, double-blind, placebo-controlled trial (Tapia et al., 2016)	Tapia	2016	Humans (Mali), phase 1, randomization and placebo	Recombinant ChAd3-GP(Zaire), 10 to 100 billion VP, boost D97 recombinant MVA-GP (Zaire + Sudan + Marburg) + NP (Taï Forest) 200 millions PFU, IM	Antibodies anti GP, D28
Ebola virus-like particle-based vaccine protects nonhuman primates against lethal Ebola virus challenge (Warfield et al., 2007)	Warfield	2007	NHP: cynomolgus macaques; placebo	VLP GP/VP40/NP(Zaire), 2 injections (42 days apart), boost D42, IM, 250 μg	Antibodies anti virion, D42
Vaccinating captive chimpanzees to save wild chimpanzees (Warfield et al., 2014)	Warfield	2014	NHP: chimpanzee; no placebo	VLP (with adjuvant: IDC-1001 ou CpG) GP/VP40/NP(Zaire), 2 injections (29 days apart), boost D27, IM, 3 mg	Antibodies anti GPΔTM or VP40, between D27 and D29, results in EC50
Homologous and heterologous protection of nonhuman primates by Ebola and Sudan virus-like particles (Warfield et al., 2015)	Warfield	2015	NHP: cynomolgus macaques; placebo	VLP GP/VP40/NP(Zaire et/ou Sudan), boost D42, IM, 3 mg	Antibodies anti GPΔTM or VP40, between D14 and D28
Immune parameters correlate with protection against ebola virus infection in rodents and nonhuman primates (Wong et al., 2012)	Wong	2012	NHP: cynomolgus macaques; placebo	Recombinant VSV-GP(Zaire Mayinga), single injection, IM or IT or PO, 20 millions PFU	Antibodies anti GP, D28
An Adenovirus Vaccine Expressing Ebola Virus Variant Makona Glycoprotein Is Efficacious in Guinea Pigs and Nonhuman Primates (Wu et al., 2016)	Wu	2016	NHP: cynomolgus macaques; placebo	Recombinant Ad5-GP(Zaire Makona), single injection, IM, 40 or 200 billion VP	Antibodies anti GP, D28
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 (Zhu et al., 2015)	Zhu	2015	Humans (China), phase 1, randomization and placebo	Recombinant Ad5-GP(Zaire Makona), single injection, IM, 40 to 160 billions VP	Antibodies anti GP (Makona), D28
Safety and immunogenicity of a recombinant adenovirus type-5 vector-based Ebola vaccine in healthy adults in Sierra Leone: a single-centre, randomised, double-blind, placebo-controlled, phase 2 trial (Zhu et al., 2017)	Zhu	2017	Humans (Sierra Leone), phase 2; randomization and placebo	Recombinant Ad5-GP(Zaire Makona), single injection, IM, 40 or 160 billion VP	Antibodies anti GP, D28

presented in Figure 3. The vast majority (82.4%) of human groups included 8 or more individuals, while only 6 for non-human primate groups (range 2; 22 with an average of 4.1 individuals by group).

Characteristics of nonhuman primate and human groups are described in Tables 2 and 3, respectively.

There is a wide heterogeneity of features among studies included in the systematic review. Vaccine platforms varied between studies, especially in NHP (18 different vaccine platforms in NHP groups versus 8 in human groups). The strain of Ebola virus used as vaccine insert or for the antibody detection after vaccination was also variable. For almost a third of the human

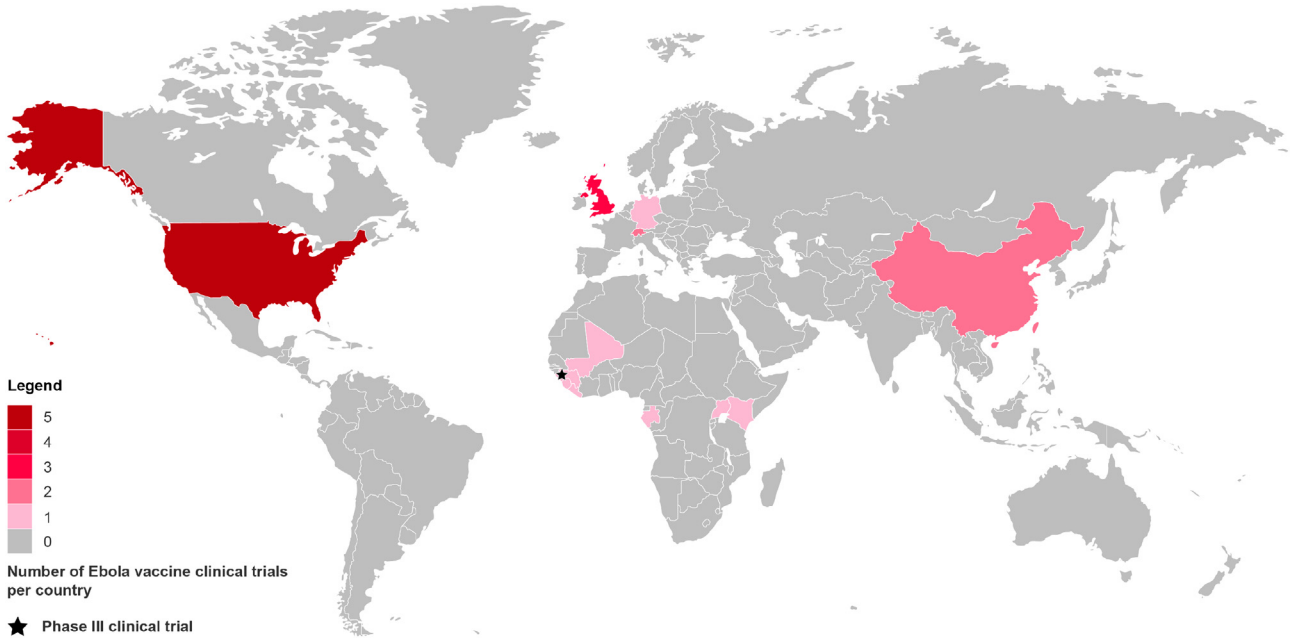

Figure 2. Description of the number of vaccine clinical trials against Ebola per country.
The Ring trial, single phase 3 trial (Guinea), has been excluded from the systematic review.
Several other vaccine clinical trials against Ebola are currently ongoing worldwide but only published trials are reported in the figure.

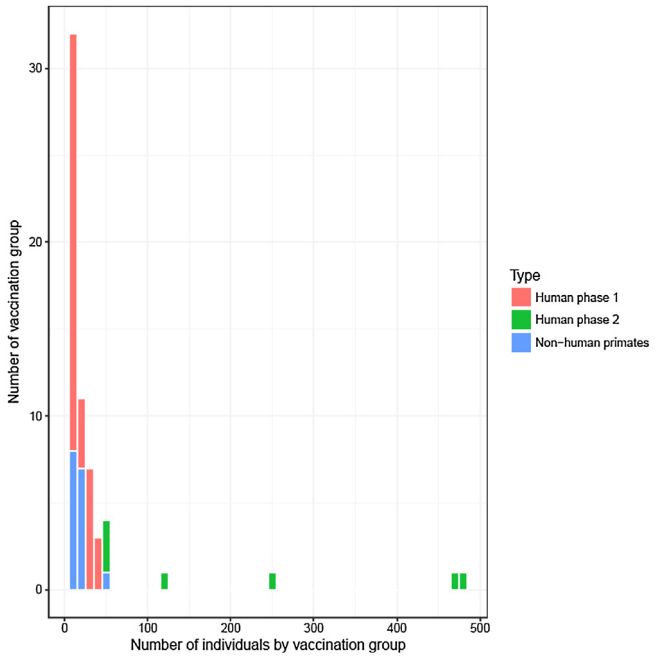

Figure 3. Number of vaccination groups of humans and of nonhuman primates, according to the number of individuals by group.

groups, the detection of antibody response was done with a heterologous strain. The time interval between the last vaccination and the antibody detection was also remarkably variable (range 3; 371 days).

Among all the 202 vaccination groups, the mean antibody titre ranged from 0 (for a group of NHP infected by the simian/human immunodeficiency virus prior to the Ebola vaccination) to 5.81 log10, with an average of 2.97 (95% CI: [2.84; 3.10]).

The NHP groups had a crude antibody response level that was significantly higher than the human groups ($p = 0.006$): in NHP groups the log10 geometric mean titre ranged from 0 to 5.81 with an average of 3.10 (95% CI: [2.93; 3.27]), and in human groups the titre ranged from 0.90 to 4.60 with an average of 2·75 (95% CI: [2.57; 2.93]) Figure S1 (appendix) shows antibody responses in human groups and in NHP groups.

Meta-regression of factors associated with variability in antibody response levels in humans and evaluation of between-groups heterogeneity

Sixty-one human vaccination groups with 8 individuals or more were included in the meta-regression analysis.

Among these, 32 were vaccinated with a low dose of vaccine, 19 with a high dose (for 10 groups, the dose category was undeterminable as only one dose level was assessed for the given vaccine platform).

The distribution of the antibody titres after Ebola vaccination per vaccination group is shown by vaccine platform in Figure 4. The antibody response seems to be higher in groups with a prime-boost strategy (Ad26/MVA or ChAd3/MVA) than in the other groups. The distribution of the antibody titres by viral strain used for antibody detection is presented in Figure S2 (appendix).

In univariate meta-regression analyses (appendix: Table S1), the antibody response after Ebola vaccination was significantly associated with the vaccine platform ($p < 0.001$), the viral strain used to detect the antibody response after vaccination ($p < 0.001$), the year of publication (for publication in 2014 and after versus before 2014: +1.15, $p < 0.001$), the mean age of vaccinated population (for ≥39 years versus <32 years: +0.90; $p < 0.001$), the vaccine dosage (for high dose versus low dose: +0.57, $p = 0.006$), the use of a vaccine boost (for boost versus no boost: +0.63, $p = 0.009$), the similarity between the viral strain used as vaccine insert and the viral strain used to detect the antibody response (for identical strains versus different strains: −0.74, $p = 0.009$), the site of the study ($p = 0.014$), the time interval between the last vaccine injection and the antibody measure (for <28 days versus ≥28 days:

Table 2
Main characteristics of included non-human primates (NHP) groups.

Characteristic	Vaccination schedule				All NHP groups	
	No boost (n = 98)		Boost (n = 30)		n = 128	
Vaccine platform						
DNA vaccine (plasmid)	6	6.1%	0	0.0%	6	4.7%
Adenovirus 26	4	4.1%	0	0.0%	4	3.1%
Adenovirus 26 then adenovirus 35	0	0.0%	1	3.3%	1	0.8%
Adenovirus 35	4	4.1%	0	0.0%	4	3.1%
Adenovirus 5	8	8.2%	3	10.0%	11	8.6%
DNA vaccine (plasmid)/adenovirus 5	0	0.0%	2	6.7%	2	1.6%
CAdVax	6	6.1%	2	6.7%	8	6.2%
Chimpanzee adenovirus 3	2	2.0%	0	0.0%	2	1.6%
Chimpanzee adenovirus 63	1	1.0%	0	0.0%	1	0.8%
HPIV3	12	12.2%	7	23.3%	19	14.8%
MVA	1	1.0%	0	0.0%	1	0.8%
NDV	1	1.0%	1	3.3%	2	1.6%
RhCMV	1	1.0%	0	0.0%	1	0.8%
Whole-virus vaccine	4	4.1%	0	0.0%	4	3.1%
VLP	21	21.4%	10	33.3%	31	24.2%
VLP Kunjin	1	1.0%	1	3.3%	2	1.6%
VRP VEEV	3	3.1%	1	3.3%	4	3.1%
VSV	23	23.5%	2	6.7%	25	19.5%
Route of administration						
Intramuscular	78	79.6%	21	70.0%	99	77.3%
Other routes	20	20.4%	9	30.0%	29	22.7%
Vaccine insert: Ebola species						
Monovalent Zaire	63	64.3%	17	56.7%	80	62.5%
Monovalent no Zaire	6	6.1%	2	6.7%	8	6.2%
Monovalent no Zaire + monovalent Zaire	0	0.0%	1	3.3%	1	0.8%
Monovalent no Zaire + multivalent	0	0.0%	1	3.3%	1	0.8%
Multivalent	29	29.6%	7	23.3%	36	28.1%
Multivalent + monovalent Zaire	0	0.0%	2	6.7%	2	1.6%
Vaccine insert: Ebola strain (only for Zaire species)						
Mayinga	34	64.2%	13	76.5%	47	67.1%
Kikwit	16	30.2%	4	23.5%	20	28.6%
Makona	3	5.7%	0	0.0%	3	4.3%
Missing data	*45*	–	*13*	–	*58*	–
Nonhuman primates species						
Cynomolgus macaques	65	66.3%	17	56.7%	82	64.1%
Chimpanzees	10	10.2%	2	6.7%	12	9.4%
Rhesus macaques	22	22.4%	10	33.3%	32	25.0%
African green monkeys	1	1.0%	1	3.3%	2	1.6%
Year of publication						
Publication < 2014	49	50.0%	14	46.7%	63	49.2%
Publication ≥ 2014	49	50.0%	16	53.3%	65	50.8%
Time interval between last injection and antibody measure						
Mean [standard deviation]	29.1	[363]	25.5	[762]	28.3	[319]
Missing data	*3*	–	*0*	–	*3*	–
Antibody measurement method						
Maximal dilution	65	66.3%	18	60.0%	83	64.8%
Effective concentration 90 (EC90)	15	15.3%	2	6.7%	17	13.3%
Effective concentration 50 (EC50)	18	18.4%	10	33.3%	28	21.9%
Antigen used for antibody detection: nature						
Glycoprotein (GP)	55	56.7%	7	24.1%	62	49.2%
Other nature (virion, viral protein 40)	42	43.3%	22	75.9%	64	50.8%
Missing data	*1*	–	*1*	–	*2*	–
Antigen used for antibody detection: Ebola strain						
Mayinga	14	87.5%	8	100.0%	22	91.7%
Kikwit	2	12.5%	0	0.0%	2	8.3%
Missing data	*82*	–	*22*	–	*104*	–
Similarity between strain used as vaccine insert and strain used for antibody detection						
Identical strains	12	100.0%	8	100.0%	20	100.0%
Missing data	*86*	–	*22*	–	*108*	–

CAdVax: complex adenovirus-based vector, DNA: deoxyribonucleic acid, GP: glycoprotein, HPIV3: human parainfluenza virus 3, MVA: modified vaccinia Ankara, NDV: Newcastle disease virus, RhCMV: rhesus cytomegalovirus cytomegalovirus, VLP: virus-like particles, VRP VEEV: Venezuelan equine encephalitis virus replicon particle, VSV: vesicular stomatitis virus.

Table 3
Main characteristics of included human groups.

Characteristics	Vaccination schedule				All human groups	
	No boost (n = 48)		Boost (n = 26)		(n = 74)	
Vaccine platform						
DNA vaccine (plasmid)	9	18.8%	1	3.8%	10	13.5%
Adenovirus 26	3	6.2%	0	0.0%	3	4.1%
Adenovirus 26/MVA or MVA/adenovirus 26	0	0.0%	5	19.2%	5	6.8%
Adenovirus 5	6	12.5%	2	7.7%	8	10.8%
Chimpanzee adenovirus 3	14	29.2%	0	0.0%	14	18.9%
Chimpanzee adenovirus 3/MVA	0	0.0%	18	69.2%	18	24.3%
MVA	2	4.2%	0	0.0%	2	2.7%
VSV	14	29.2%	0	0.0%	14	18.9%
Route of administration						
Intramuscular	48	100.0%	26	100.0%	74	100.0%
Vaccine insert: species						
Monovalent Zaire	31	64.6%	19	73.1%	50	67.4%
Monovalent Zaire + multivalent	0	0.0%	4	15.4%	4	5.4%
Multivalent	17	35.4%	1	3.8%	18	24.3%
Multivalent + monovalent Zaire	0	0.0%	2	7.7%	2	2.7%
Vaccine insert: strain (only for Zaire species)						
Mayinga	22	71.0%	22	91.7%	44	80.0%
Kikwit	5	16.1%	0	0.0%	5	9.1%
Makona	4	12.9%	0	0.0%	6	10.9%
Missing data	*17*	–	*4*	–	*19*	–
Proportion of women						
Mean [standard deviation]	40%	[18%]	52%	[10%]	44%	[17%]
Mean age (years)						
Mean [standard deviation]	34.8	[45]	34.6	[54]	34.7	[48]
Geographic location of the study						
Africa	14	29.2%	1	3.8%	15	20.3%
China	2	4.2%	2	7.7%	4	5.4%
Europe	15	31.2%	22	84.6%	37	50.0%
USA	17	35.4%	1	3.8%	18	24.3%
Year of publication						
Publication < 2014	8	16.7%	0	0.0%	8	10.8%
Publication ≥ 2014	40	83.3%	26	100.0%	66	89.2%
Time interval between last injection and antibody measure (days)						
Mean [standard deviation]	31.2	[220]	26.1	[32]	29.3	[179]
Antibody measurement method						
Maximal dilution	35	72.9%	24	92.3%	59	79.7%
Effective concentration 90 (EC90)	13	27.1%	2	7.7%	15	20.3%
Antigen used for antibody detection: nature						
Glycoprotein (GP)	45	93.8%	25	96.2%	70	94.6%
Other nature (virion, nucleoprotein)	3	6.2%	1	3.8%	4	5.4%
Antigen used for antibody detection: Ebola strain						
Mayinga	14	36.8%	16	72.7%	30	50.0%
Kikwit	18	47.4%	5	22.7%	23	38.3%
Makona	6	15.8%	1	4.5%	7	11.7%
Missing data	*10*	–	*4*	–	*14*	–
Similarity between strain used as vaccine insert and strain used for antibody detection						
Different strains	9	32.1%	6	27.3%	15	30.0%
Identical strains	19	67.9%	16	72.7%	35	70.0%
Missing data	*20*	–	*4*	–	*24*	–

CAdVax: complex adenovirus-based vector, DNA: deoxyribonucleic acid, GP: glycoprotein, HPIV3: human parainfluenza virus 3, MVA: modified vaccinia Ankara, NDV: Newcastle disease virus, RhCMV: rhesus cytomegalovirus cytomegalovirus, VLP: virus-like particles, VRP VEEV: Venezuelan equine encephalitis virus replicon particle, VSV: vesicular stomatitis virus.

+0.70, p = 0.021), and the Ebola species of vaccine insert (for multivalent and other species versus monovalent Zaire: −0.47, p = 0.027).

Alone, the vaccine platform was the factor which explained the largest part of heterogeneity among all the studied factors (R^2 for vaccine platform = 55%). For all the univariate models, the heterogeneity was very high with I^2 ranging from 97% to 99%.

Results of the final multivariate meta-regression model are shown in Table 4. High heterogeneity was found with a I^2 of 95% and a R^2 of 68%, even after adjustment on the factors associated

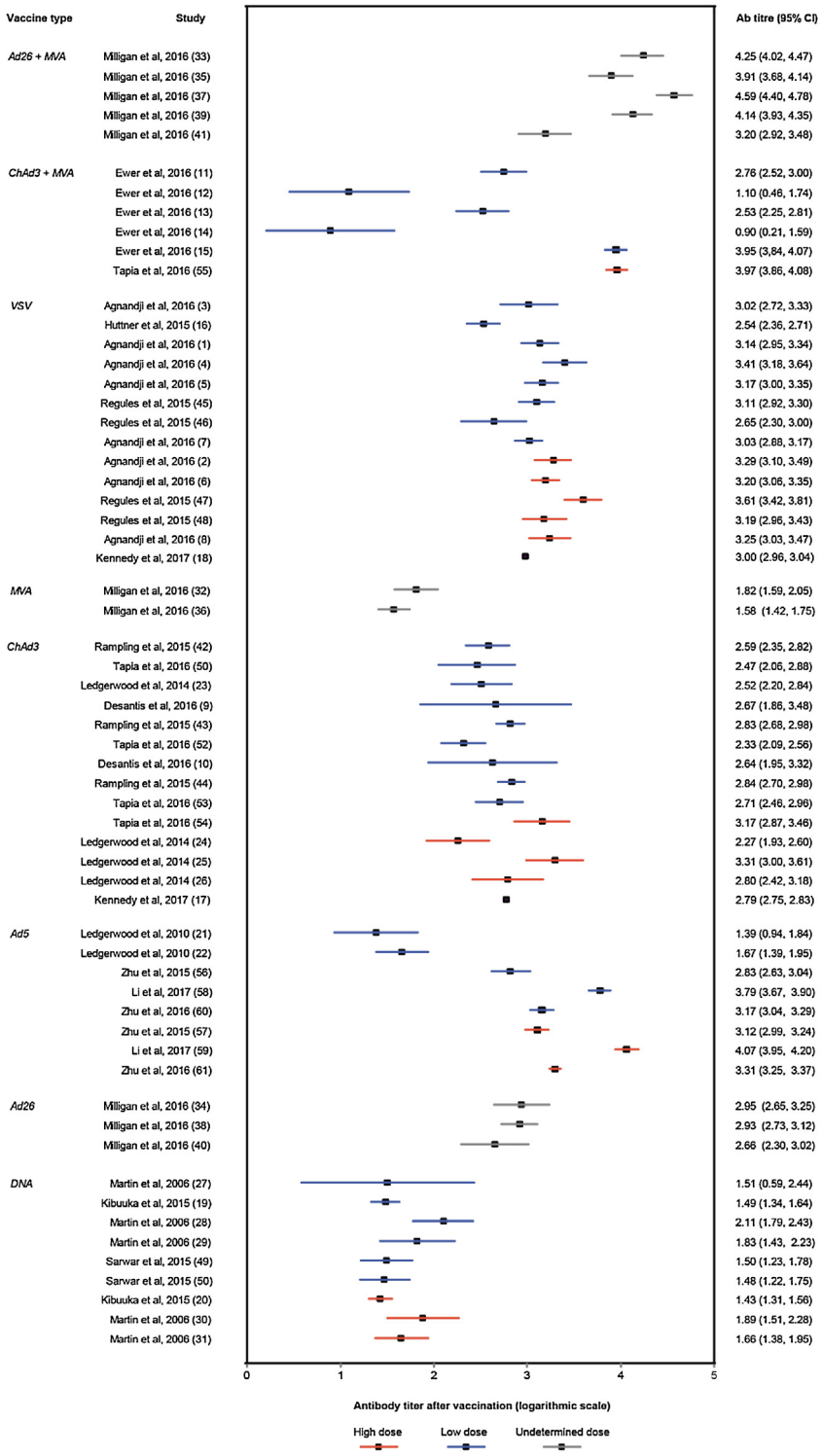

Figure 4. Forest plot of antibody titre after Ebola vaccination for each vaccination group by vaccine platform. Colour codes indicate dose levels within a given platform. GP: glycoprotein. PFU: plaque forming unit. VP: viral particle. TCID: tissue culture infectious dose.

References for Figure 4:

1: Agnandji 2016, VSV vaccine (3.10^6 PFU) with Zaire insert, Germany, detection with Zaire Kikwit GP
2: Agnandji 2016, VSV vaccine (2.10^7 PFU) with Zaire insert, Germany, detection with Zaire Kikwit GP
3: Agnandji 2016, VSV vaccine (3.10^5 PFU) with Zaire insert, Gabon, detection with Zaire Kikwit GP
4: Agnandji 2016, VSV vaccine (3.10^6 PFU) with Zaire insert, Gabon, detection with Zaire Kikwit GP
5: Agnandji 2016, VSV vaccine (3.10^6 PFU) with Zaire insert, Kenya, detection with Zaire Kikwit GP
6: Agnandji 2016, VSV vaccine (2.10^7 PFU) with Zaire insert, Kenya, detection with Zaire Kikwit GP
7: Agnandji 2016, VSV vaccine (1.10^7 PFU) with Zaire insert, Switzerland, detection with Zaire Kikwit GP
8: Agnandji 2016, VSV vaccine (5.10^7 PFU) with Zaire insert, Switzerland, detection with Zaire Kikwit GP
9: De Santis 2016, ChAd3 vaccine ($2.5.10^{10}$ VP) with Zaire Mayinga insert, Switzerland, detection with Zaire Mayinga GP
10: De Santis 2016, ChAd3 vaccine (5.10^{10} VP) with Zaire Mayinga insert, Switzerland, detection with Zaire Mayinga GP

with antibody response in this final model. This emphasises the lack of factors that explained the antibody response among the variables included in the model.

Vaccine platform and viral strain used for detection were the two factors which were independently associated with antibody response after vaccination against Ebola. Compared to the MVA vaccine platform, the recombinant vaccines using DNA or Ad26 (associated or not with an injection of MVA vaccine), ChAd3or VSV vectors were significantly associated with a higher antibody response after vaccination (more than 1.2 log10 units more compared to MVA alone). The statistical association between the vaccine platform and the antibody response was strong and consistent regardless of which other variables were included in the model (sensitivity analyses, data not shown). The antibody response using Makona strain for antibody detection was significantly higher than with use of Mayinga strain (1 log10 unit more compared to the Mayinga strain). By contrast, the antibody response with Kikwit detection strain was not significantly different from the ones with Mayinga strain.

The vaccine dosage, analysed as a binary variable of high versus low dose in the present analyses, was not found to be associated with antibody response variability. Different classifications were tested for this variable (same threshold across the different vaccine platforms corresponding to the mean dose level for categorizing into “low-dose” and “high-dose” groups, classification into three categories, classification of groups with undifferentiated dosages into “low-dose” or into “high-dose” groups), but the dosage was never significant in the multivariate models in these sensitivity analyses (data not shown), nor was the interaction between dose and vaccine platform.

In additional sensitivity analyses, a full model including all variables significantly associated with the antibody response in univariate models (i.e. with no forward selection procedure) did not modify heterogeneity ($I^2 = 92\%$) compared to the model

11: Ewer 2016, ChAd3 vaccine ($2.5.10^{10}$ VP) with Zaire Mayinga insert + boost MVA vaccine at D7 ($1.5.10^{8}$ PFU) with multivalent insert, United Kingdom (UK), detection with Zaire Mayinga GP (Jenner method)
12: Ewer 2016, ChAd3 vaccine ($2.5.10^{10}$ VP) with Zaire Mayinga insert + boost MVA vaccine at D7 ($1.5.10^{8}$ PFU) with multivalent insert, UK, detection with Zaire Mayinga GP (ADI method)
13: Ewer 2016, ChAd3 vaccine ($2.5.10^{10}$ VP) with Zaire Mayinga insert + boost MVA vaccine at D14 ($1.5.10^{8}$ PFU) with multivalent insert, UK, detection with Zaire Mayinga GP (Jenner method)
14: Ewer 2016, ChAd3 vaccine ($2.5.10^{10}$ VP) with Zaire Mayinga insert + boost MVA vaccine at D14 ($1.5.10^{8}$ PFU) with multivalent insert, UK, detection with Zaire Mayinga GP (ADI method)
15: Ewer 2016, ChAd3 vaccine (1 to 5.10^{10} VP) with Zaire Mayinga insert + boost MVA vaccine ($1.5.10^{8}$ PFU) with multivalent insert, UK, detection with Zaire Makona virion
16: Huttner 2015, VSV vaccine (3.10^{5} PFU) with Zaire insert, Switzerland, detection with Zaire Kikwit GP
17: Kennedy 2017, ChAd3 vaccine (2.10^{11} PU) with Zaire insert, Liberia
18: Kennedy 2017, VSV vaccine (2.10^{7} PFU) with Zaire insert, Liberia
19: Kibuuka 2015, 3 injections of DNA vaccine (4 mg) with multivalent insert, Uganda, detection with Zaire GP
20: Kibuuka 2015, 3 injections of DNA vaccine (8 mg) with multivalent insert, Uganda, detection with Zaire GP
21: Ledgerwood 2010, Ad5 vaccine (2.10^{9} VP) with multivalent insert, USA, detection with Zaire GP
22: Ledgerwood 2010, Ad5 vaccine (2.10^{10} VP) with multivalent insert, USA, detection with Zaire GP
23: Ledgerwood 2014, ChAd3 vaccine (2.10^{10} PU) with multivalent insert, USA, detection with Zaire Mayinga GP
24: Ledgerwood 2014, ChAd3 vaccine (2.10^{10} PU) with multivalent insert, USA, detection with Zaire Makona GP
25: Ledgerwood 2014, ChAd3 vaccine (2.10^{11} PU) with multivalent insert, USA, detection with Zaire Mayinga GP
26: Ledgerwood 2014, ChAd3 vaccine (2.10^{11} PU) with multivalent insert, USA, detection with Zaire Makona GP
27: Li 2017, 2 injections of Ad5 vaccine (4.10^{10} VP) with Zaire Makona insert, China
28: Li 2017, 2 injections of Ad5 vaccine ($1.6.10^{11}$ VP) with Zaire Makona insert, China
29: Martin 2006, 3 injections of DNA vaccine (2 mg) with multivalent insert, USA, detection with Zaire NP
30: Martin 2006, 3 injections of DNA vaccine (4 mg) with multivalent insert, USA, detection with Zaire GP
31: Martin 2006, 3 injections of DNA vaccine (4 mg) with multivalent insert, USA, detection with Zaire NP
32: Martin 2006, 3 injections of DNA vaccine (8 mg) with multivalent insert, USA, detection with Zaire GP
33: Martin 2006, 3 injections of DNA vaccine (8 mg) with multivalent insert, USA, detection with Zaire NP
34: Milligan 2016, MVA vaccine (10^{8} TCID50) with multivalent insert, UK, detection with Zaire Kikwit GP
35: Milligan 2016, MVA vaccine (10^{8} TCID50) with multivalent insert + boost Ad26 vaccine at D28 (5.10^{10} VP) with Zaire Mayinga insert, UK, detection with Zaire Kikwit GP
36: Milligan 2016, Ad26 vaccine (5.10^{10} VP) with Zaire Mayinga insert, UK, detection with Zaire Kikwit GP
37: Milligan 2016, Ad26 vaccine (5.10^{10} VP) with Zaire Mayinga insert + boost MVA vaccine at D28 (10^{8} TCID50) with multivalent insert, UK, detection with Zaire Kikwit GP
38: Milligan 2016, MVA vaccine (10^{8} TCID50) with multivalent insert, UK, detection with Zaire Kikwit GP
39: Milligan 2016, MVA vaccine (10^{8} TCID50) with multivalent insert + boost Ad26 vaccine at D56 (5.10^{10} VP) with Zaire Mayinga insert, UK, detection with Zaire Kikwit GP
40: Milligan 2016, Ad26 vaccine (5.10^{10} VP) with Zaire Mayinga insert, UK, detection with Zaire Kikwit GP
41: Milligan 2016, Ad26 vaccine (5.10^{10} VP) with Zaire Mayinga insert + boost MVA vaccine at D56 (10^{8} TCID50) with multivalent insert, UK, detection with Zaire Kikwit GP
42: Milligan 2016, Ad26 vaccine (5.10^{10} VP) with Zaire Mayinga insert, UK, detection with Zaire Kikwit GP
43: Milligan 2016, Ad26 vaccine (5.10^{10} VP) with Zaire Mayinga insert + boost MVA vaccine at D14 (10^{8} TCID50) with multivalent insert, UK, detection with Zaire Kikwit GP
44: Rampling 2015, ChAd3 vaccine (10^{10} VP) with Zaire Mayinga insert, UK, detection with Zaire GP
45: Rampling 2015, ChAd3 vaccine ($2.5.10^{10}$ VP) with Zaire Mayinga insert, UK, detection with Zaire GP
46: Rampling 2015, ChAd3 vaccine (5.10^{10} VP) with Zaire Mayinga insert, UK, detection with Zaire GP
47: Regules 2015, VSV vaccine (3.10^{6} PFU) with Zaire Kikwit insert, USA, detection with Zaire Kikwit GP
48: Regules 2015, VSV vaccine (3.10^{6} PFU) with Zaire Kikwit insert, USA, detection with Zaire Mayinga GP
49: Regules 2015, VSV vaccine (2.10^{7} PFU) with Zaire Kikwit insert, USA, detection with Zaire Kikwit GP
50: Regules 2015, VSV vaccine (2.10^{7} PFU) with Zaire Kikwit insert, USA, detection with Zaire Mayinga GP
51: Sarwar 2015, 3 injections of DNA vaccine (4 mg) with multivalent insert, USA, detection with Zaire GP
52: Sarwar 2015, 4 injections of DNA vaccine (4 mg) with multivalent insert, USA, detection with Zaire GP
53: Tapia 2016, ChAd3 vaccine (10^{10} VP) with Zaire insert, Mali, detection with Zaire GP
54: Tapia 2016, ChAd3 vaccine ($2.5.10^{10}$ VP) with Zaire insert, Mali, detection with Zaire GP
55: Tapia 2016, ChAd3 vaccine (5.10^{11} VP) with Zaire insert, Mali, detection with Zaire GP
56: Tapia 2016, ChAd3 vaccine (10^{12} VP) with Zaire insert, Mali, detection with Zaire GP
57: Tapia 2016, ChAd3 vaccine (10^{10} to 10^{12} VP) with Zaire insert + boost MVA vaccine at D97 (2.10^{8} PFU) with multivalent insert, Mali, detection with Zaire GP
58: Zhu 2015, Ad5 vaccine (4.10^{10} VP) with Zaire Makona insert, China, detection with Zaire Makona GP
59: Zhu 2015, Ad5 vaccine ($1.6.10^{11}$ VP) with Zaire Makona insert, China, detection with Zaire Makona GP
60: Zhu 2016, Ad5 vaccine (4.10^{10} VP) with Zaire Makona insert, Sierra Leone, detection with Zaire Makona GP
61: Zhu 2016, Ad5 vaccine ($1.6.10^{11}$ VP) with Zaire Makona insert, Sierra Leone, detection with Zaire Makona GP

Table 4
Results of a random-effect meta-regression model (with fixed intragroup variance) of determinants of antibody titre (log10) after Ebola vaccination according to characteristics of vaccine, population, and measurement techniques. Multivariate analysis. $I^2 = 95.31\%$, $R^2 = 68.45\%$.

Determinants of antibody response	Estimated β [CI 95%]		p value
Vaccine platform (reference: MVA vaccine)			**<0.001**
DNA	0.43	[−0.52; 1.37]	0.379
Ad26	1.15	[033; 197]	0.006
Ad26/MVA or MVA/Ad26	2.32	[158; 307]	<0.001
Ad5	0.54	[−0.42; 1.50]	0.268
ChAd3	0.97	[010; 183]	0.028
ChAd3/MVA	0.81	[−0.13; 1.76]	0.091
VSV	1.46	[079; 213]	<0.001
Viral strain used for antibody detection (reference: Mayinga strain)			**<0.001**
Kikwit	0.30	[−0.27; 0.86]	0.301
Makona	0.99	[050; 148]	<0.001

presented above. In the full model, the vaccine platform was significantly associated with the antibody response ($p = 0.002$), but the viral strain used to detect the antibody response after vaccination was not ($p = 0.996$). The other variables were not associated with the antibody response.

Discussion

This systematic review on preventive Ebola vaccine trials has found 49 studies conducted in humans or in NHP. The meta-analysis, using a random-effect inverse variance meta-regression including 61 human vaccination groups, showed a major part of antibody response variability in humans that remained unexplained by the factors included in the model. Indeed, the between-group heterogeneity I^2 exceeded 90%, even after adjustment for the factors associated with antibody response. Two significant determinants were independently associated with antibody response after preventive vaccination against EVD: the Ebola vaccine platform and the Ebola strain used for antibody detection.

The use of a systematic review methodology, including solicitation of experts, allowed us to conduct exhaustive descriptive analyses on all Ebola vaccinated groups in NHP or humans published in the literature up to January 2017. Our descriptive results showed an extreme variability of study designs and features, especially in nonhuman primate trials. This variability is related to the recentness of the research topic. The higher variability within nonhuman primate studies compared to human trials is easily explained by the process of vaccine development, which selects for further clinical trials only the subset of candidate vaccines proven to be immunogenic in nonhuman primates. The comparison of antibody response levels between humans and nonhuman primate only had an indicative purpose. It is indeed difficult to compare these very different models, mostly because of potential multiple confounding factors.

Due to the low sample size of each group of nonhuman primates, we decided to restrict heterogeneity analyses to human groups. Human groups with small sample size were excluded, since their between-group variance would have been too low to contribute to the meta-regression model. It was not possible to pool small groups together because of high heterogeneity in the factors likely to influence the antibody response (vaccine and population characteristics, and measure of antibody response). The threshold of at least 8 individuals per group allowed us to include the majority of human groups in the meta-regression. Sensitivity analyses using a threshold of 10 individuals led to the same final results.

The very high heterogeneity between vaccination groups could be explained by various reasons. Firstly, some factors influencing the antibody response may be missing, for instance, genetic factors that are influencing the immunogenicity of the vaccines (Sridhar, 2015). Secondly, the analysis of grouped data, due to unavailability of individual data for the groups included in our meta-regression model, led to a lack of precision in the estimation of influence of factors on antibody response, and also in the evaluation of antibody response heterogeneity across vaccination groups. Thirdly, the enzyme-linked immunosorbent assay (ELISA) measuring relative antibody concentration of immunoglobulin G against EBOV glycoprotein used in the different trials could have a variation of its precision (Logue et al., 2018). Lastly, the extreme variability of study designs certainly explains parts of the high between-group variance for antibody response observed in our results.

Despite the major between-group heterogeneity in our meta-regression model, two factors significantly associated with antibody response variability could be identified. The Ebola strain used for antibody detection seems to influence the results of ELISA tests. This demonstrates the importance of harmonisation for the measurement methods used in vaccines evaluations, and highlights the difficulty in directly comparing published results across several trials. The Ebola vaccine platform was also strongly associated with antibody response.

For the other factors studied in our meta-analysis, no association was found with the antibody response variability. In particular, the vaccine dosage did not have any significant influence on the level of the antibody response in our results. We acknowledge that the use of a binary variable may have limited the ability to detect a dose-effect in the meta-regression. However, the regression result is consistent with the descriptive results that also did not suggest a clear dose-immunogenicity relationship within a given vaccine platform.

No population characteristic was independently associated with the antibody response after Ebola vaccination. It may be possible that the low diversity of the population, which is directly related to the strict criteria for selection of trial participants, prevented the identification of a potential impact of these population characteristics on the antibody response.

Conclusion

Our findings show that there are still significant uncertainties in the determinants of the antibody response after preventive vaccination against Ebola virus disease. This emphasises the interest of harmonizing measurement methods and study designs. Furthermore, it indicates the impossibility to directly compare results from one published study to another or to extrapolate results, due to considerable variations in studies features. Assessment of immunogenicity between Ebola vaccines needs randomised controlled multi-arm trials, as performed in PREVAIL study (NCT02344407) and PREVAC study (NCT02876328).

Conflict of interest

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No. 115861 This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation program and EFPIA.

Laura Richert and Rodolphe Thiebaut are also involved in the ongoing PREVAC (NCT02876328) and Ebovac2 (NCT02564523, NCT02416453) trials. Edouard Lhomme is involved in the PREVAC trial (NCT02876328).

Funding source

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115861. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Ethical considerations

According to the National Public Health Code, review and meta-analysis do not require ethical approval.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2018.06.022.

References

Agnandji ST, Huttner A, Zinser ME, Njuguna P, Dahlke C, Fernandes JF, et al. Phase 1 trials of rVSV Ebola vaccine in Africa and Europe. N Engl J Med 2016;374(17):1647–60.

Bukreyev A, Rollin PE, Tate MK, Yang L, Zaki SR, Shieh W-J, et al. Successful topical respiratory tract immunization of primates against Ebola virus. J Virol 2007;81(June (12)):6379–88.

Bukreyev AA, Dinapoli JM, Yang L, Murphy BR, Collins PL. Mucosal parainfluenza virus-vectored vaccine against Ebola virus replicates in the respiratory tract of vector-immune monkeys and is immunogenic. Virology 2010;399(2):290–8.

De Santis O, Audran R, Pothin E, Warpelin-Decrausaz L, Vallotton L, Wuerzner G, et al. Safety and immunogenicity of a chimpanzee adenovirus-vectored Ebola vaccine in healthy adults: a randomised, double-blind, placebo-controlled, dose-finding, phase 1/2a study. Lancet Infect Dis 2016;16(3):311–20.

Dhama K, Malik YS, Malik SVS, Singh RK. Ebola from emergence to epidemic: the virus and the disease, global preparedness and perspectives. J Infect Dev Ctries 2015;9(5):441–55.

DiNapoli JM, Yang L, Samal SK, Murphy BR, Collins PL, Bukreyev A. Respiratory tract immunization of non-human primates with a Newcastle disease virus-vectored vaccine candidate against Ebola virus elicits a neutralizing antibody response. Vaccine 2010;29(1):17–25.

Ebola Situation Report—30 March 2016 | Ebola [Internet]. [Cited 4 January 2017]. Available from: http://apps.who.int/ebola/current-situation/ebola-situation-report-30-march-2016.

Ewer K, Rampling T, Venkatraman N, Bowyer G, Wright D, Lambe T, et al. A monovalent chimpanzee adenovirus ebola vaccine boosted with MVA. N Engl J Med 2016;374(17):1635–46.

Food and Drug Administration. Licensure of Ebola vaccines: demonstration of effectiveness [Internet]. 2015 Available from: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM445819.pdf.

Geisbert TW, Daddario-Dicaprio KM, Geisbert JB, Reed DS, Feldmann F, Grolla A, et al. Vesicular stomatitis virus-based vaccines protect nonhuman primates against aerosol challenge with Ebola and Marburg viruses. Vaccine 2008a;26(52):6894–900.

Geisbert TW, Daddario-Dicaprio KM, Lewis MG, Geisbert JB, Grolla A, Leung A, et al. Vesicular stomatitis virus-based ebola vaccine is well-tolerated and protects immunocompromised nonhuman primates. PLoS Pathog 2008b;4(11)e1000225.

Geisbert TW, Geisbert JB, Leung A, Daddario-DiCaprio KM, Hensley LE, Grolla A, et al. Single-injection vaccine protects nonhuman primates against infection with marburg virus and three species of ebola virus. J Virol 2009;83(14):7296–304.

Geisbert TW, Bailey M, Hensley L, Asiedu C, Geisbert J, Stanley D, et al. Recombinant adenovirus serotype 26 (Ad26) and Ad35 vaccine vectors bypass immunity to Ad5 and protect nonhuman primates against ebolavirus challenge. J Virol 2011;85(9):4222–33.

Grant-Klein RJ, Altamura LA, Badger CV, Bounds CE, Van Deusen NM, Kwilas SA, et al. Codon-optimized filovirus DNA vaccines delivered by intramuscular electroporation protect cynomolgus macaques from lethal Ebola and Marburg virus challenges. Hum Vaccines Immunother 2015;11(8):1991–2004.

Henao-Restrepo AM, Camacho A, Longini IM, Watson CH, Edmunds WJ, Egger M, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!). Lancet 2017;389(10068):505–18.

Hensley LE, Mulangu S, Asiedu C, Johnson J, Honko AN, Stanley D, et al. Demonstration of cross-protective vaccine immunity against an emerging pathogenic Ebolavirus species. PLoS Pathog 2010;6(5)e1000904.

Herbert AS, Kuehne AI, Barth JF, Ortiz RA, Nichols DK, Zak SE, et al. Venezuelan equine encephalitis virus replicon particle vaccine protects nonhuman primates from intramuscular and aerosol challenge with ebolavirus. J Virol 2013;87(9):4952–64.

Huttner A, Dayer J-A, Yerly S, Combescure C, Auderset F, Desmeules J, et al. The effect of dose on the safety and immunogenicity of the VSV Ebola candidate vaccine: a randomised double-blind, placebo-controlled phase 1/2 trial. Lancet Infect Dis 2015;15(10):1156–66.

Jones SM, Feldmann H, Ströher U, Geisbert JB, Fernando L, Grolla A, et al. Live attenuated recombinant vaccine protects nonhuman primates against Ebola and Marburg viruses. Nat Med 2005;11(7):786–90.

Kennedy SB, Bolay F, Kieh M, Grandits G, Badio M, Ballou R, et al. Phase 2 placebo-controlled trial of two vaccines to prevent ebola in Liberia. N Engl J Med 2017;377:1438–47.

Kibuuka H, Berkowitz NM, Millard M, Enama ME, Tindikahwa A, Sekiziyivu AB, et al. Safety and immunogenicity of Ebola virus and Marburg virus glycoprotein DNA vaccines assessed separately and concomitantly in healthy Ugandan adults: a phase 1b, randomised, double-blind, placebo-controlled clinical trial. Lancet 2015;385(9977):1545–54.

Ledgerwood JE, Costner P, Desai N, Holman L, Enama ME, Yamshchikov G, et al. A replication defective recombinant Ad5 vaccine expressing Ebola virus GP is safe and immunogenic in healthy adults. Vaccine 2010;29(2):304–13.

Ledgerwood JE, Sullivan NJ, Graham BS. Chimpanzee adenovirus vector ebola vaccine–preliminary report. N Engl J Med 2015;373(8):776.

Li J-X, Hou L-H, Meng F-Y, Wu S-P, Hu Y-M, Liang Q, et al. Immunity duration of a recombinant adenovirus type-5 vector-based Ebola vaccine and a homologous prime-boost immunisation in healthy adults in China: final report of a randomised, double-blind, placebo-controlled, phase 1 trial. Lancet Glob Health 2017;5(3):e324–34.

Liu WB, Li ZX, Du Y, Cao GW. Ebola virus disease: from epidemiology to prophylaxis. Mil Med Res 2015;2:7.

Logue J, Tuznik K, Follmann D, Grandits G, Marchand J, Reilly C, et al. Use of the Filovirus Animal Non-Clinical Group (FANG) Ebola virus Immuno-assay requires fewer study participants to power a study than the Alpha Diagnostic International assay. J Virol Methods 2018;255:84–90.

Martin JE, Sullivan NJ, Enama ME, Gordon IJ, Roederer M, Koup RA, et al. A DNA vaccine for Ebola virus is safe and immunogenic in a phase I clinical trial. Clin Vaccine Immunol 2006;13(11):1267–77.

Marzi A, Engelmann F, Feldmann F, Haberthur K, Shupert WL, Brining D, et al. Antibodies are necessary for rVSV/ZEBOV-GP-mediated protection against lethal Ebola virus challenge in nonhuman primates. Proc Natl Acad Sci U S A 2013;110(5):1893–8.

Marzi A, Feldmann F, Geisbert TW, Feldmann H, Safronetz D. Vesicular stomatitis virus–based vaccines against lassa and ebola viruses. Emerg Infect Dis 2015a;21(2):305–7.

Marzi A, Halfmann P, Hill-Batorski L, Feldmann F, Shupert WL, Neumann G, et al. Vaccines. An Ebola whole-virus vaccine is protective in nonhuman primates. Science 2015b;348(6233):439–42.

Marzi A, Robertson SJ, Haddock E, Feldmann F, Hanley PW, Scott DP, et al. Ebola vaccine. VSV-EBOV rapidly protects macaques against infection with the 2014/15 Ebola virus outbreak strain. Science 2015c;349(6249):739–42.

Marzi A, Murphy AA, Feldmann F, Parkins CJ, Haddock E, Hanley PW, et al. Cytomegalovirus-based vaccine expressing Ebola virus glycoprotein protects nonhuman primates from Ebola virus infection. Sci Rep 2016;6:21674.

Matassov D, Marzi A, Latham T, Xu R, Ota-Setlik A, Feldmann F, et al. Vaccination with a highly attenuated recombinant vesicular stomatitis virus vector protects against challenge with a lethal dose of ebola virus. J Infect Dis 2015;212 Suppl 2:S443–51.

Meyer M, Garron T, Lubaki NM, Mire CE, Fenton KA, Klages C, et al. Aerosolized Ebola vaccine protects primates and elicits lung-resident T cell responses. J Clin Invest 2015;125(8):3241–55.

Milligan ID, Gibani MM, Sewell R, et al. Safety and immunogenicity of novel adenovirus type 26—and modified vaccinia ankara—vectored ebola vaccines: a randomized clinical trial. JAMA 2016;315(15):1610–23.

Mire CE, Geisbert JB, Marzi A, Agans KN, Feldmann H, Geisbert TW. Vesicular stomatitis virus-based vaccines protect nonhuman primates against Bundibugyo ebolavirus. PLoS Negl Trop Dis 2013;7(12)e2600.
Mire CE, Matassov D, Geisbert JB, Latham TE, Agans KN, Xu R, et al. Single-dose attenuated Vesiculovax vaccines protect primates against Ebola Makona virus. Nature 2015;520(7549):688–91.
Ohimain EI. Recent advances in the development of vaccines for Ebola virus disease. Virus Res 2016;211:174–85.
Pratt WD, Wang D, Nichols DK, Luo M, Woraratanadharm J, Dye JM, et al. Protection of nonhuman primates against two species of Ebola virus infection with a single complex adenovirus vector. Clin Vaccine Immunol 2010;17(4):572–81.
Pyankov OV, Bodnev SA, Pyankova OG, Solodkyi VV, Pyankov SA, Setoh YX, et al. A Kunjin Replicon virus-like particle vaccine provides protection against Ebola virus infection in nonhuman primates. J Infect Dis 2015;212 Suppl 2:S368–71.
Rampling T, Ewer K, Bowyer G, Wright D, Imoukhuede EB, Payne R, et al. A monovalent chimpanzee adenovirus Ebola vaccine—preliminary report. N Engl J Med 2015;374(17):1635–46.
Regules JA, Beigel JH, Paolino KM, Voell J, Castellano AR, Muñoz P, et al. A recombinant vesicular stomatitis virus ebola vaccine—preliminary report. N Engl J Med 2015;376(4):330–41.
Sarwar UN, Costner P, Enama ME, Berkowitz N, Hu Z, Hendel CS, et al. Safety and immunogenicity of DNA vaccines encoding Ebolavirus and Marburgvirus wild-type glycoproteins in a phase I clinical trial. J Infect Dis 2015;211(4):549–57.
Sridhar S. Clinical development of Ebola vaccines. Ther Adv Vaccines 2015;3(5–6):125–38.
Stanley DA, Honko AN, Asiedu C, Trefry JC, Lau-Kilby AW, Johnson JC, et al. Chimpanzee adenovirus vaccine generates acute and durable protective immunity against ebolavirus challenge. Nat Med 2014;20(10):1126–9.
Sullivan NJ, Sanchez A, Rollin PE, Yang ZY, Nabel GJ. Development of a preventive vaccine for Ebola virus infection in primates. Nature 2000a;408(6812):605–9.
Sullivan NJ, Sanchez A, Rollin PE, Yang ZY, Nabel GJ. Development of a preventive vaccine for Ebola virus infection in primates. Nature 2000b;408(6812):605–9.
Sullivan NJ, Geisbert TW, Geisbert JB, Xu L, Yang Z-Y, Roederer M, et al. Accelerated vaccination for Ebola virus haemorrhagic fever in non-human primates. Nature 2003;424(6949):681–4.
Sullivan NJ, Martin JE, Graham BS, Nabel GJ. Correlates of protective immunity for Ebola vaccines: implications for regulatory approval by the animal rule. Nat Rev Microbiol 2009;7(5):393–400.
Sullivan NJ, Hensley L, Asiedu C, Geisbert TW, Stanley D, Johnson J, et al. CD8+ cellular immunity mediates rAd5 vaccine protection against Ebola virus infection of nonhuman primates. Nat Med 2011;17(9):1128–31.
Swenson DL, Wang D, Luo M, Warfield KL, Woraratanadharm J, Holman DH, et al. Vaccine to confer to nonhuman primates complete protection against multistrain Ebola and Marburg virus infections. Clin Vaccine Immunol 2008;15(3):460–7.
Tapia MD, Sow SO, Lyke KE, Haidara FC, Diallo F, Doumbia M, et al. Use of ChAd3-EBO-Z Ebola virus vaccine in Malian and US adults, and boosting of Malian adults with MVA-BN-Filo: a phase 1, single-blind, randomised trial, a phase 1b, open-label and double-blind, dose-escalation trial, and a nested, randomised, double-blind, placebo-controlled trial. Lancet Infect Dis 2016;16(1):31–42.
Van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med 2002;21(4):589–624.
Warfield KL, Swenson DL, Olinger GG, Kalina WV, Aman MJ, Bavari S. Ebola virus-like particle-based vaccine protects nonhuman primates against lethal Ebola virus challenge. J Infect Dis 2007;196 Suppl 2:S430–7.
Warfield KL, Goetzmann JE, Biggins JE, Kasda MB, Unfer RC, Vu H, et al. Vaccinating captive chimpanzees to save wild chimpanzees. Proc Natl Acad Sci U S A 2014;111(24):8873–6.
Warfield KL, Dye JM, Wells JB, Unfer RC, Holtsberg FW, Shulenin S, et al. Homologous and heterologous protection of nonhuman primates by Ebola and Sudan virus-like particles. PLoS One 2015;10(3)e0118881.
Wong G, Richardson JS, Pillet S, Patel A, Qiu X, Alimonti J, et al. Immune parameters correlate with protection against ebola virus infection in rodents and nonhuman primates. Sci Transl Med 2012;4(158)158ra146.
World Health Organisation. Correlates of vaccine-induced protection: methods and implications. 2013.
Wu X-X, Yao H-P, Wu N-P, Gao H-N, Wu H-B, Jin C-Z, et al. Ebolavirus vaccines: progress in the fight against Ebola virus disease. Cell Physiol Biochem 2015;37(5):1641–58.
Wu S, Kroeker A, Wong G, He S, Hou L, Audet J, et al. An adenovirus vaccine expressing Ebola virus variant makona glycoprotein is efficacious in guinea pigs and nonhuman primates. J Infect Dis 2016;214(Suppl. 3):S326–32.
Zhu F-C, Hou L-H, Li J-X, Wu S-P, Liu P, Zhang G-R, et al. 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. Lancet 2015;385(9984):2272–9.
Zhu F-C, Wurie AH, Hou L-H, Liang Q, Li Y-H, Russell JBW, et al. Safety and immunogenicity of a recombinant adenovirus type-5 vector-based Ebola vaccine in healthy adults in Sierra Leone: a single-centre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet 2017;389(10069):621–8.