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

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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

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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).