Assessment of Chimpanzee Adenovirus Serotype 63 Neutralizing Antibodies Prior to Evaluation of a Candidate Malaria Vaccine Regimen Based on Viral Vectors

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Prior to a chimpanzee adenovirus-based (ChAd63) malarial vaccine trial, sera were collected to assess ChAd63-specific neutralizing antibody titers in Banfora (Burkina Faso). The low neutralizing antibody titers reported in both adults and children (median titers, 139.1 and 35.0, respectively) are encouraging for the potential use of ChAd63 as a malarial vaccine vector.

Malaria viral vectored-based vaccines provide a means by which to rapidly activate the host innate immune system simultaneously with the delivery of malaria antigen-expressing genes without the requirement of additional adjuvants. Viral vectors can also be used to overcome the manufacturing hurdles that accompany mosquito- and/or sporozoite-based vaccine formulations and produce a high titer relatively easily.

Replication-incompetent adenovirus vector-based vaccines have been proven to be immunogenic and have been evaluated in clinical trials (1–3). The adaptive immune responses to the vector may potentially block or reduce the induction of the desired responses against the vaccine antigen. This has given rise to concerns about the usefulness of such vaccines in target populations in which the majority of people have preexisting anti-vector immunity to serotypes that have been used as vectors (4). However, the levels of antibodies to chimpanzee viruses appear to be low in humans in Africa and elsewhere (4–8), and this has been confirmed recently for the ChAd63 strain in Kenyan children and in the Gambia (9, 10).

The purpose of this study was to quantify the prevalence of neutralizing antibodies to ChAd63 in a population likely to benefit from a viral vector malarial vaccine, who were living in an area of Burkina Faso that is endemic for malaria.

The study volunteers were drawn from a cohort study carried out at the Banfora trial site (western Burkina Faso). The site was chosen for an upcoming viral vector malarial vaccine trial, utilizing ChAd63 followed by boosting with modified vaccinia Ankara (MVA), both expressing the multiple epitope-thrombospondin-related adhesion protein (ME-TRAP) construct that has been shown to be highly immunogenic and confer some T-cell-mediated protective efficacy against controlled human malaria infection (CHMI) (11). The study participants were 100 children age 0.5 to 3 years and 100 volunteers age 10 to 45 years who were randomly selected from 600 samples they initially provided for this purpose.

This study was approved by the institutional review board of the Centre National de Recherche et de Formation sur le Paludisme (Ouagadougou, Burkina Faso).

The sera were stored at −80°C prior to the measurement of ChAd63-neutralizing antibodies titers at the Jenner Institute Laboratories at the University of Oxford (United Kingdom) using a secreted alkaline phosphatase (SEAP) quantitation assay, as described previously (8). Statistical analyses were performed with Excel and Stata version 9.0 software (College Station, TX, USA).

The lower limit of the neutralizing antibodies against the ChAd63-SEAP titer range measured was 17 arbitrary units attributed to negative samples <1:18, which is the lowest dilution limit of the assay, and the highest dilution titer was 2,144.

In Fig. 1, the median value of neutralizing antibody titers was 35.0 (interquartile range [IQR], 24.0 to 71.0) in children age 0.5 to 3 years, while in adults, it was 139.1 (IQR, 66.8 to 380.0). The difference in the median values between adults and children was statistically significant (P < 0.0001).

In order to compare these results with those of previous publications, we focused presenting results on those individuals having a clinically relevant neutralizing titer (defined as a 50% neutralization titer > 200) (10). Among the study participants, 77% had antibody titers of <200. However, 97.0% of children had a titer of <200, compared with 57% adults having a titer of <200. Three children with antibody titers of >200 were >2 years old.

Virus-neutralizing antibodies induced by adenoviral infections or upon adenoviral vector delivery are primarily directed against the surface loops of the viral hexon (12), although antibodies to the penton base or the fiber can also neutralize adenovirus (13).

A large proportion of human adults possess significant titers of neutralizing antibodies to common human serotypes. Neutralizing antibodies have the potential to reduce the potency of viral vector vaccines by inhibiting vector-mediated delivery of the encoded transgene. Recently, the issue of preexisting anti-vector immunity has been addressed through the development of new vectors based on serotypes to which the human population is less exposed, including those of chimpanzee origin (9, 14–16). Chimpanzee adenoviral vectors have been shown to be highly immuno-
genic in animal models (17, 18) and recently in clinical malarial vaccine trials (1, 2).

From the data generated in this study, it appears that very few children had antibody titers against the chimpanzee adenovirus ChAd63 above the clinically significant threshold of 200. Our findings are not an exception and are consistent with the results from other African countries that are endemic for malaria. In Kilifi (eastern Kenya), similar findings showed that only 3% of children from age 1 to 6 years had neutralizing antibody levels (i.e., titers of >200), compared with 3% in our study children age 0.5 to 3 years (9). Similarly, neutralizing antibody titers of adenoviruses of chimpanzee origin were generally much lower in human serum samples from other studies (10, 19).

However, in the group age >10 years old, a higher prevalence of high-titer serum neutralization against ChAd63 was observed. As suggested previously, it is unclear whether these preexisting neutralizing antibodies are caused by cross-reactivity to ChAd63 of antibodies induced by a closely related human adenovirus or by a low prevalence of ChAd63 infections in humans (1).

This is the first report of data on chimpanzee adenovirus neutralizing antibodies in Burkina Faso and is timely due to the initiation of a phase I/IIb clinical trial of a malarial vaccine candidate based on chimpanzee adenovirus vector serotype 63. Although a higher prevalence of mid- to high-titer neutralizing antibodies to ChAd63 in adults was reported, the low frequency of high-titer neutralizing antibodies to ChAd63 in children, who are the target group for vaccination, is very encouraging for its potential use as a malarial vaccine vector. Furthermore, it was recently reported that neutralizing antibodies to ChAd63 do not impact vaccine immunogenicity and efficacy in human immunized volunteers (11).

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Correction for Nébié et al., Assessment of Chimpanzee Adenovirus Serotype 63 Neutralizing Antibodies Prior to Evaluation of a Candidate Malaria Vaccine Regimen Based on Viral Vectors

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Volume 21, no. 6, p. 901–903, 2014. Page 902, column 1: The following paragraph was inadvertently omitted from the Acknowledgments section.

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