Reviewer's report

Title: The association between the ratio of monocytes:lymphocytes at age 3 months and risk of tuberculosis (TB) in the first two years of life.

Version: 1 Date: 2 April 2014

Reviewer: Markus Maeurer

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The authors analyze the association of monocyte / lymphocyte ratio in the risk to develop clinical TB. This is a very interesting study that takes up earlier observations concerning the role of monocytes and (potential) markers for immune protection / risk for TB.

Several points should be addressed (compulsory):

1. Please rephrase the statements in the manuscript, they are unclear and difficult to read:
   1.a. Recent whole genome transcript studies (Fletcher et al., submitted), historic[3-82 5] and recent animal studies[6, 7], and recent studies in human adults[8] all suggest that the ratio of monocytes:lymphocytes in peripheral blood may be associated with subsequent mycobacterial disease outcomes.

   Please break down the sentences in individual statements and comment on the outcome of each study cited, since this is the key issue of the report.

   1b: In support of the ML ratio being on the causal pathway for TB development, 225 are the plausibility, gradient, temporality, consistency with experimental 226 animal and observational adult studies, coherence with in vitro findings and 227 apparent specificity in that the association is strongest between ML ratio and 228 development of definite/probable TB. In opposition is the modest effect size. 229 Further studies should endeavor to assess more detailed subsets of 230 monocytes and lymphocytes to identify precise cellular players in this

   The reader gets lost with the statements here. Please rephrase if and cut it in digestable pieces, i.e. what has been shown and what is the biological / clinical meaning for the interpretation of your data.

2. '....Latent MTB infection
   131 amongst HIV-uninfected infants was diagnosed by tuberculin skin testing at
132 approximately 2, 3, and 4 years of age, or when clinically indicated. The
133 criteria used for categorizing TB as either possible, probable or
microbiologic…'

Please clarify the background here. Latent TB was diagnosed by a positive skin
test - Is that considered indeed to be indicative of latent TB in children? what is
the clinical meaning of a positive skin test in the area where the study has been
conducted? Could it be that individuals have been exposed, the skin test is
positive and yet there is no latent TB? Please clarify this point and discuss here
studies that support the information.

3. The report is based on statistical analysis and modeling outlined in the
materials and methods section.

'......Where possible we preferred modeling continuous variables as
145 fractional polynomials[10, 11], an approach that allows continuous variables
146 to be analyzed on their native scale without categorization, and allowing for
147 non-linear fits. Scaled Schoenfeld residuals were inspected to evaluate the
148 proportionality assumptions. All statistical tests were two-sided at the 5%
149 significance level.. Poisson approximations were used to calculate
150 confidence intervals(CIs) for estimations of the incidence rate. Bootstrapped
151 estimates of the adjusted HR across the ML ratio continuum were generated
152 with the ‘boot’ package…' This may sound clear for a statistician, yet not for
the reader unfamiliar with the field. Please explain step by step each method; use
supplementary data sets if necessary for more explanations if needed. Please
make clear what you like to achieve / address with each methods.

4. Monocytes can also be infected by HIV and this is associated with the HIV
variants. Do you have information on the HIV population in each patient and the
level of HIV+ monocytes (associated with the tropism of the HIV isolate)? This is
part of the core of this report. Please discuss also the interacton of HIV with
monocytes and their potential functional impairment.

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: Yes, but I do not feel adequately qualified to assess the
statistics.

Declaration of competing interests:

I declare that I have no competing interests.