COMMENT: REVERSAL REACTION IN MULTIBACILLARY LEPROSY PATIENTS FOLLOWING MDT WITH AND WITHOUT IMMUNOTHERAPY WITH A CANDIDATE FOR AN ANTILEPROSY VACCINE, *MYCOBACTERIUM W*. H. K. KAR *ET AL.*

Sir,

It was with much interest that I read the above paper published in *Lepr Rev* (1993) **64,** 219–26. The immunotherapy described holds promise, and in particular the apparent rapid clearing of *Mycobacterium leprae* from the tissues is a very interesting phenomenon. It is also commendable that Kar *et al.* have not only thought of the possibility that such therapy might increase the risk of reversal reaction, but that they have actually set up a trial to investigate this possibility. The conclusion they draw from the trial seems reassuring: the difference between the proportions of patients that developed a reversal reaction in each group, 22·6% in the vaccine group *vs* 15·1% in the control group, was not statistically significant. Similarly, the proportion of severe reactions was only 'marginally higher' in the vaccine group (43·7% *vs* 33·3%). This leads the authors to conclude, 'Thus, the vaccine did not precipitate *any* additional neurological complication—an important observation in the context of introducing an immunemodulator' [italics mine].

I fully agree that the latter observation is essential not only when introducing an immunemodulator, but for any new leprosy treatment that is introduced.[1] The problem with the above study is that they *did* find an increase in risk of reaction over a 2-year period of 7·5% overall, 10·3% in the BL/LL group and 10·4% in risk of severe reaction. These differences were not statistically significant *with the given sample size*, which was only 53 patients in each group.

'Significantly' (the *z*-value) of any given difference is proportional to the sample size: a small sample size is likely to give a nonsignificant result and a bigger sample size increases the chance of finding a significant difference if it truly exists. This can be illustrated using the number of reactions observed in the above study. If the whole study had been 10 times as big, the observed number of reactions in the vaccine group would have been 120/530 (22·6%); in the control group 80/530 (15·1%). The difference would still be 7·5%, the *z*-value is now 3·12, corresponding to a *p*-value of 0·0018, a highly significant result! The difference in the BL/LL group would have been 80/390 *vs* 40/390, giving a *z*-value of 3·99, $p < 0{\cdot}0001$. The conclusion of the study would have been very different. The relative risk of vaccine *vs* control would have been 1·50 (1·13–1·97). This means that the vaccine seems to be associated with an increase in the risk of reversal reaction of 50% (95% confidence interval 13–97%). It would be unlikely that the authors would have concluded that the vaccine 'can be safely used'.

For a study such as conducted by Kar *et al.* the required sample size should be calculated in advance on the basis of the minimum difference that is clinically relevant to detect. The formula giving the sample size *in each of the trial groups* in the case of a difference between proportions is:[2]

$$n = \frac{p_1 \times (1 - p_1) + p_2 \times (1 - p_2)}{(p_2 - p_1)^2} \times f_{(\alpha,\beta)}$$

where p_1 is the proportion in the control group, p_2 is the proportion in the intervention group (in this case the vaccine group), and $f_{(\alpha,\beta)}$ is a constant value that depends on the type I and type II

error size that is acceptable.[2] Usually, these are 5% and 20%, which correspond to an *f*-value of 7·9. Thus, if we say that it would be important to detect a 7·5% increase in risk of reversal reaction (as in the above study), the equation would read:

$$n = \frac{0{\cdot}151 \times (1 - 0{\cdot}151) + 0{\cdot}226 \times (1 - 0{\cdot}226)}{(0{\cdot}226 - 0{\cdot}151)^2} \times 7{\cdot}9 = 426$$

We would, therefore, need 426 patients in each group, or more than 8 times the study size of the above study! With the given group size of 53 even an increase in risk of 15% in the vaccine group would not have been significant at the 5% level.

Since this 'adjuvant' vaccine would potentially be used on a large scale, caution is called for. If, say, 10,000 BB, BL and LL patients were to be treated with the vaccine, this might result in an *extra* 750 cases of reversal reaction. Applying the 'neuritis proportion' found in the study (25%) then 188 patients would have a severe reaction with neuritis, needing steroid treatment. Kar *et al.* report that 1 patient out of 7 (14%) failed to recover on steroid treatment and needed reconstructive surgery. This corresponds with our experience, but may be a conservative estimate (the failure rate being higher under operational conditions). Applied to the above numeric example, 26 patients would need reconstructive surgery as a result of the vaccine.

This may be a far too pessimistic a view since the actual increase in risk due to the vaccine may well be lower than 7·5%. The reported data are, after all, compatible with the null hypothesis of no difference between the groups. But the point is that we cannot tell, the results did not *prove* the null hypothesis, they just failed to reject it.

A much larger trial (preferably done blind) is therefore urgently called for, before this vaccine can be used on a large scale on the basis of an unjustified sense of safety.

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References

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[2] Pocock SJ. Clinical Trials. *A practical approach.* John Wiley & Sons (Publ), Chichester, 1988.