

HIV vaccines: good news or bad? Elisabeth Pisani. <http://www.wisdomofwhores.com/2009/10/28/hiv-vaccines-good-news-or-bad/>

The paper reviewed on the preceding page¹ has received much media attention, and has featured in Elisabeth Pisani's blog, 'Sex and Science'. I felt it could be helpful to Journal readers if I also reviewed some of the concerns about the HIV vaccine paper² that were detailed in that blog.

Dr Pisani's blog focuses mainly on specific aspects of the HIV vaccine trial paper:² approaches taken to statistical analysis, observed variation in vaccine efficacy (VE) in some subgroups (such as high-risk individuals), and the public health perspective.

The three analyses undertaken in the paper are termed Real World [Intention to Treat (ITT)], Ideal World (per protocol) and Tidied-up World (modified ITT). Dr Pisani states that the Real World analysis is most useful to public health policymakers, which is usually correct. However, in this case it would mean wilful acceptance of a misleading estimate of VE, because in this analysis the two groups compared included unequal numbers of individuals who had already become infected *before* vaccination commenced, and for whom infection could *not* be prevented. That said, this criticism is something of a diversion, or blog filler – the estimates obtained by the three analyses are strikingly similar, a VE of around 26% to 31%. Would a vaccine of such efficacy be of clinical use?

Attention is drawn to the wide confidence intervals (CIs) around the estimates of VE. This is an important point and, as has been commented above,¹ would have benefited from some discussion by the authors. However, this issue is perhaps over-laboured. In all trial papers the point estimate reported is likely to be accompanied by an interval estimate, which argues for a more circumspect assessment of plausible possibilities for true effect, and often some of these possibilities are clinically trivial. While it is true that this trial

has turned out to be underpowered, and hence provides very imprecise estimates of effect, we still need to give the point estimate due consideration.

Having disparaged, on account of their wide CIs, the overall effect estimates from the two planned and one modified analysis approaches, Dr Pisani then focuses on the effect estimate for the high-risk subgroup, and laments the VE estimate of only 4% in this subgroup, "the people most likely to be exposed to the virus". However, this subgroup involves only 23% of all study participants, and more crucially involves only 34% of events ($n = 45$), compared to 100% and 65% of events in the planned analyses, and 95% in the modified ITT. This partly explains the width of the 95% CI reported for VE for the high-risk group, which is -73% to $+46\%$. So, while the width of the CIs for the main analyses reported are, respectively, 52, 65 and 52 percentage points, that for the high-risk group is 119 percentage points – *twice* as wide! If we are to bear in mind that the true overall VE in the modified ITT analysis might be as low as 1% (the lower limit of the CI), then we should be equally careful to bear in mind that the true VE in the high-risk group might be as high as 46% (the upper limit). Subgroup analyses are of great interest to all scientists, have the potential to generate new and insightful research questions, and will usually be of great help in the design of future research. However, subject as these smaller subgroups are to additional sampling variability, they provide notoriously unreliable estimates. [For another example of potential instability of estimates across subgroups, it is reported, but not commented on by Pisani, that for the age group 21–25 years VE is 49% (95% CI 13–70).] Furthermore, tests of heterogeneity (of treatment effect across subgroups) are inevitably much lower powered even than the overall test of treatment effect. In fact the paper reports in passing that all tests of subgroup factors are non-significant.² This could be interpreted as *no difference* in VE between high-risk group and lower-risk groups, which might

provide solace to Dr Pisani. However, a more circumspect view is that the study just does not have the power to test the association between risk group (or age group) and VE (as the authors in fact state). In the light of the concerns expressed in this blog regarding the VE for the high-risk group, it seems that perhaps the authors should have provided a clear 'public health warning' along with the subgroup table.

Having raised concerns about various aspects of the research and its reporting – these mainly founded on the uncertainty inherent to some degree or other, in (all) research results, and on the cumbersome and counter-intuitive nature of the hypothetico-deductive reasoning required – Dr Pisani goes on to conclude that the trial is a "triumph for science", if not yet for public health. It is salutary to recognise a distinction between the 'science' stage, and the 'public health' stage of vaccine development and implementation, but such 'science' needs to remember that its driving force is the imperative for a future public health application. Dr Pisani was astute in highlighting in her blog that the report of the trial did not pay sufficient attention to the public health perspective of its findings.

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References

- 1 Warner P. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand (Journal Review). *J Fam Plann Reprod Health Care* 2010; **36**: 46.
- 2 Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, et al.; for the MOPH-TAVEG Investigators. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med* 20 October 2009; 10.1056/NEJMoa0908492.

MEETINGS AND COURSES

6 March 2010

Title: Northern Interbranch Spring Update. **Venue:** Tankersley Manor, Tankersley, Barnsley S75 3DQ, UK. **Details:** Topics include female genital mutilation, an update on the changes to the latest UKMEC Guidelines, a review of the evidence for the safe use of Depo-Provera in different client groups, followed by workshops reviewing complex or difficult case studies of clients using LARCS. **Accreditation:** FSRH applied for. **Information:** Dr Jenny Manuel, 28 The Spinney, Moortown, Leeds LS17 6SP, UK. E-mail: Jennifer.manuel@nhs.net.

11–12 March 2010

Title: BMS – FSRH Menopause Special Skills Module. **Venue:** Holiday Inn, Birmingham City Centre, UK. **Details:** This course is practical and interactive in design, based on the workshop style of the FSRH Diploma course. It is aimed at doctors but would equally be suitable for specialist nurses who work regularly to provide women's health advice and management. It intends to equip the clinician to work within a menopause clinic or primary care environment. Further training would be required to lead a specialist service. **Accreditation:** FSRH accredited, 13 hours CME. **Information:** Mike Gray, Crescetus, Eglosme Farm, St Erme, Truro, Cornwall TR4 9BW, UK. Tel: +44 (0) 1872 242192. Fax: +44 (0) 1872 242197. E-mail: info@crescetus.com. Website: www.crescetus.co.uk.

19–20 April 2010

Title: Letter of Competence in Medical Education (LocMED). **Venue:** Welsh Institute for Women's Health, Cardiff Medicentre, Heath Park, Cardiff, UK. **Details:** Applications are invited from

Diplomates of the Faculty of Sexual and Reproductive Healthcare who are actively involved in contraception and reproductive healthcare, equivalent to 100 sessions in the past year. **Accreditation:** 10/01. **Information:** Mrs Deborah Jenkins, Welsh Institute for Women's Health, Cardiff Medicentre, University Hospital of Wales, Heath Park, Cardiff CF14 4UJ, UK. Tel: +44 (0) 29 2075 8587. E-mail: wihwdeb@btinternet.com.

19–22 May 2010

Title: 11th Congress of the European Society of Contraception and Reproductive Health on "Culture, Communication, Contraception". **Venue:** World Forum Convention Centre, The Hague, The Netherlands. **Details:** The title of the congress reflects that contraceptive and reproductive health care in multicultural Europe must address the different needs of different individuals in different situations. There is a growing requirement for preventive strategies that take into account the specific cultural, subcultural, economic, ethnic and religious characteristics of subpopulations within the European community. It is the diversity of multicultural Europe that challenges our creativity to provide new solutions, new methods and innovative approaches. **Accreditation:** a maximum of 15 European CME credits. **Information:** ESC Central Office, Opalfeneweg 3, 1740 Ternat, Belgium. Tel: +32 2 582 08 52. Fax: +32 2 582 55 15. E-mail: congress@contraception-esc.com. Website: www.contraception-esc.com/thehague.htm.

9 July 2010

Title: Abortion Care Theory Course. **Venue:** Hexham General Hospital, Hexham,

Northumberland, UK. **Details:** One-day theory course for the Certificate in Abortion Care of the Faculty of Sexual and Reproductive Healthcare. **Information:** Mr M Mansour, Holtburn, 6 Well Road, Stocksfield, Northumberland NE43 4QW, UK. Tel: +44 (0) 1661 843675. E-mail: m.mansour@nhs.net.

7–8 October 2010

Title: BMS – FSRH Menopause Special Skills Module. **Venue:** Crown Plaza Hotel, Leeds, UK. **Details:** This course is practical and interactive in design, based on the workshop style of the FSRH Diploma course. It is aimed at doctors but would equally be suitable for specialist nurses who work regularly to provide women's health advice and management. It intends to equip the clinician to work within a menopause clinic or primary care environment. Further training would be required to lead a specialist service. **Accreditation:** FSRH accredited, 13 hours CME. **Information:** Mike Gray (see 11–12 March 2010 entry).

25–26 November 2010

Title: BMS – FSRH Menopause Special Skills Module. **Venue:** Holiday Inn, Southampton, UK. **Details:** This course is practical and interactive in design, based on the workshop style of the FSRH Diploma course. It is aimed at doctors but would equally be suitable for specialist nurses who work regularly to provide women's health advice and management. It intends to equip the clinician to work within a menopause clinic or primary care environment. Further training would be required to lead a specialist service. **Accreditation:** FSRH accredited, 13 hours CME. **Information:** Mike Gray (see 11–12 March 2010 entry).