Up Close: The meta-analysis of Ad5 candidates

In 2013 the vaccine field grappled with the results of a meta-analysis of data from trials evaluating vaccine strategies that included a vector based on adenovirus serotype 5 (Ad5). In scientific terms, a meta-analysis pools together data from multiple clinical trials of the same treatment or intervention—or of multiple similar treatments or interventions. This approach is used to systematically and quantitatively review the data on a given topic. By combining data, meta-analyses may sometimes allow for a more definitive conclusion about a topic, since larger data sets can allow for more precision, as well as exploration across sub-groups.

The analysis, conducted by Peter Gilbert and colleagues at the HIV Vaccine Trials Network, looked at infections in the vaccine and placebo arms of the Step, Phambili and HVTN 505 trials. Pooling data from these trials, there were 200 infections among participants who received at least one injection of the vaccine; there were 147 infections in the comparable placebo group. Overall, this translated into a 33 percent elevated risk in vaccine recipients compared with placebo recipients. No trend to higher risk of HIV infection was seen in HVTN 505. When the data from this trial were excluded, the vaccine-associated risk in Step and Phambili rose to 41percent.

The Ad5 strategy tested in HVTN 505 contained synthetic fragments of HIV envelope (the outer coating of the virus). The vaccines in Step and Phambili did not. It is possible that immune responses targeting *env* elicited by the HVTN 505 vaccine may have mitigated the risk seen in the other two Ad5 trials. There is discussion now about whether *env* should be consistently used as a vaccine insert based on these data.

Like all meta-analyses, this one has limitations. By definition it was conducted post-hoc (it wasn't planned before the trials were launched), and it isn't as statistically conclusive as it might be if there were larger data sets. Step and Phambili data are not directly comparable. Step participants were in the trial for much longer than Phambili participants—and much of the data from Phambili was collected after participants learned whether they had received the vaccine or the placebo. Overall, 80 percent of infections were in men—primarily men who were uncircumcised and had pre-existing antibodies to Ad5. The available data suggest that there was more enhancement in men than women— and one proposal for mitigating risk is to move other Ad candidates forward in women first. But the numbers are small. Even with these limitations, the meta-analysis is being taken seriously as an indication that the Ad5 candidate in Step and Phambili affected risk of HIV infection. This development is an absolute worst-case scenario for the field. Upcoming vaccine trials, like the RV144 follow-on trials, will vigilantly monitor for both harm and efficacy.