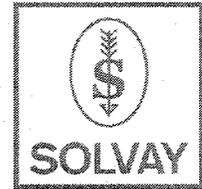


The European CHMP criteria for influenza vaccine immunogenicity cannot be improved by the use of confidence intervals.

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Annual update studies

Every year, the WHO recommends strain compositions for influenza vaccines in order to be up to date regarding circulating epidemic virus strains. In the EU, influenza vaccine manufacturers are required to file clinical data on the immunogenicity and safety of the new composition. The details of the clinical study and the criteria for evaluating the results are outlined in a CHMP Note for Guidance¹. Two groups of at least 50 subjects are to be studied: healthy adults and elderly. For every subject pre- and post-vaccination HI antibody titers are determined to assess the efficacy of the vaccine. From these three parameters are derived: the seroprotection and the seroconversion rate and the mean fold increase. For adults the seroprotection rate must exceed 70%, the seroconversion rate 40% and the mean fold increase 2.5; the respective limits for elderly are 60%, 30% and 2.0. To meet the CHMP requirement for immunogenicity, for both age groups and all three virus strains in the vaccine at least one of these criteria must be met.

Improving the CHMP criteria

It is sometimes argued that the Note for Guidance can be improved by introducing more stringent criteria. For example, that the lower bounds of the two-sided 95%-confidence intervals for the parameters must exceed the limits set by the CHMP, instead of the estimates of the parameters themselves. The motivation for this proposal being that if, for instance, the seroprotection rate exceeds 70%, this does not prove that the true seroprotection level in the target population also exceeds the limit. But if the lower confidence bound falls above the limit we can be confident that the true level does exceed 70%.

Theory...

Confidence intervals for single group means are interpretable only if the subjects constitute a random sample from a well-defined population.

Practice...

In annual update studies this is not the case. To make the two target populations – adults and elderly – less abstract, we add the restriction that the subjects must be inhabitants of a member state of the EU, and willing to be vaccinated. The seroprotection rate is a proportion: the number of subjects with a post-vaccination HI titer greater or equal to 40, divided by the total number of vaccinated subjects. Suppose that a GP practice in for instance the Netherlands calls on healthy adults to participate in an influenza vaccination study, and that in this way a group of 50 volunteers is recruited. We cannot claim that this group is a random or even a "representative" sample from the adult target population. Firstly, the subjects were not chosen at random from the target population – in fact, they were not chosen at random at all. Secondly, the age distribution of the subjects will most likely deviate from that of the target population, and age is an important determinant of the immune response.

Quote²:

"It is a curious vice, of which even statisticians are frequently guilty, to calculate standard errors of group means from clinical trials. Such standard errors are more or less ritually calculated by taking the standard deviation and dividing by the square root of the sample size. This formula, which everybody learns at 'Stat 1' at university, is justified by simple random sampling, a thing which never happens in connection with clinical trials and could never (...)"

²Stephen Senn. *Statistics in Medicine* 2004; 23: 3729-53.

What does the seroprotection rate quantify?

Not the fraction of the adult target population that would become seroprotected if vaccinated. Because the subjects are not a random sample from the population. Likewise, the confidence interval for the seroprotection rate is not an interval estimate of a population fraction. Neither the rate nor the confidence interval quantifies anything. The seroprotection rate is the fraction of subjects in the study who became seroprotected, no more, no less.

And that is why

The CHMP criteria for influenza vaccine immunogenicity cannot be improved by the use of confidence intervals.

Acknowledging this, we could raise the following question:

Why have faith in the CHMP criteria?

The answer is: if for a group of subjects the criterion for, say, seroprotection is met, this is *qualitative* proof of vaccine immunogenicity. If the vaccine induces adequate antibody responses in at least 70% of a group of unselected subjects – unselected in the sense that they were not chosen because of their expected immune response –, and given the current knowledge of the immune system and the wealth of experience with vaccinations, we can be confident it will induce also adequate responses in a large fraction of the population.

References

1. Committee for Proprietary Medicinal Products: Note for Guidance on Harmonisation of Requirements for Influenza Vaccines, 1997.
2. Stephen Senn. Added Values. Controversies concerning randomization and additivity in clinical trials. *Statistics in Medicine* 2004; 23: 3729-53.