A long story made too short: surrogate variables and the communication of HPV vaccine trial results

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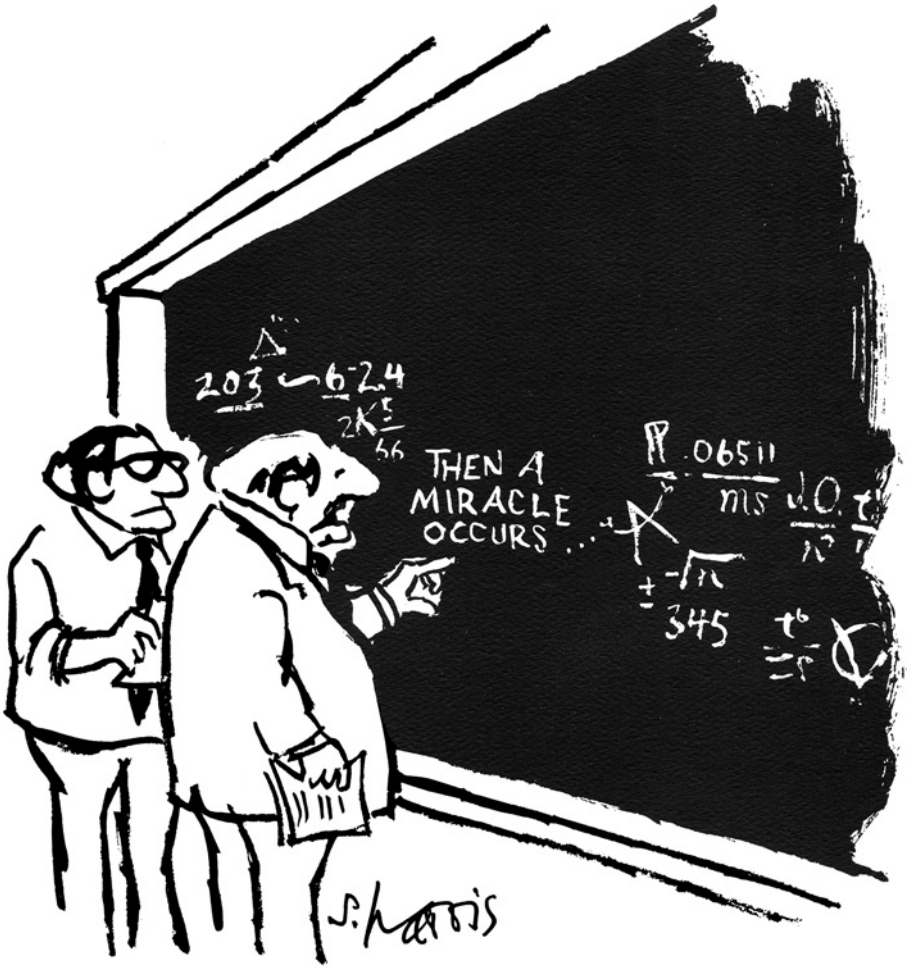
The story of epidemiologists and surrogate variables is one of a classic love–hate relationship. Epidemiologists love surrogates because many studies would not be possible without them. When events are rare or the time between an intervention and the outcome is long, surrogate variables are used to fill the gap. Epidemiologists hate surrogate variables because they introduce an additional step in the chain between intervention (or exposure) and outcome, and thus an additional source of error. To introduce surrogates means to increase uncertainty — and, perhaps, an error.

A recent "collection of misleading surrogate end points" reminds us that caution is warranted: examples from this collection include the Cardiac Arrhythmia Suppression Trial in which a group of patients with asymptomatic or mildly symptomatic ventricular arrhythmia after myocardial infarction were treated with encainide or flecainide. Both drugs are used to suppress ventricular arrhythmia (the surrogate end point), but they were actually associated with excess mortality (the relevant outcome). In another case, patients treated with fluoride developed the desired increase in bone mineral density at the lumbar spine (the surrogate end point) but suffered from a higher rate of vertebral fractures than the control group.[1] Assessing whether surrogate variables actually measure what they purport to measure (ie, for their validity) is therefore required. Available instruments, however, can only test if a surrogate correctly indicates the direction of an effect — that is, if the endpoint it stands for decreases or increases if the surrogate variable decreases or increases.[2] How the magnitude of the effect can be derived from surrogates is by far less clear. Hence, the uncertainty associated with the use of a surrogate needs to be properly discussed and communicated.

A pertinent case in point is the introduction of the vaccines against human papillomavirus (HPV), which has created controversies among scientists, women health groups and the public. One of the key questions is to what degree the HPV vaccines, Cervirax and Gardasil, contribute towards decreasing the burden of cervical cancer.[3–6] To understand the discussion about the effectiveness of these vaccines, it is helpful to look at the role that surrogates played in the clinical trials of Gardasil, FUTURE I and II.

Clearly, trials of HPV vaccines cannot wait for cervical cancers to occur but need surrogate endpoints — for example, cervical intraepithelial neoplasia of grade 2 or higher (CIN2+). In the total study population of young women aged



"I THINK YOU SHOULD BE MORE EXPLICIT HERE IN STEP TWO."

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15–26 years, the relative efficacy of the vaccine against CIN2+ was 7.8% in FUTURE I[7] and 17% in FUTURE II.[8] As the study populations comprised women who were infected with preventable HPV types, the FUTURE studies conducted statistical analyses in subgroups comprising only of women who tested negative for HPV 16 or 18 at the beginning of the study. Conceptually, this corresponds to a surrogate as well; in this case, a surrogate for the population of girls before their first sexual intercourse. In this predefined group, the relative efficacy was 27.0% in FUTURE II[8] and 16.9% in a joint analysis of three studies.[9] Furthermore, in the predefined per-protocol analysis, only CIN2+ associated with HPV types 16 and 18 in the (surrogate) group naïve to 16 or 18 were included. The relative efficacy was close to 100%. As the types 16 and 18 have been associated with 70% of all cervical cancer cases in cross-sectional studies, many proponents of HPV vaccination declared that vaccination of all girls before their first sexual intercourse would, in the long run, prevent 70% of all cervical cancer cases — yet another untested surrogate. Finally, in the FUTURE studies, a new population was defined retrospectively, consisting only of women who (also retrospectively) tested negative to almost all oncogenic HPV types at the onset of the study. Supposedly, they should constitute an even better surrogate for girls before their first sexual intercourse. However, applying this criterion led to the exclusion of about half of the original study population. The remaining group is presumably less sexually active than average, so it is difficult to tell how sound the conclusions drawn from this surrogate population are.

Theoretical considerations (eg, possible replacement by HPV types not covered by the vaccines, concurrent infections with vaccine-preventable and non-vaccine-preventable HPV types) as well as the empirical data presented above suggest that the true size of the vaccines' protective efficacy remains unknown. The crucial question is, can we simply extrapolate the proportion of cervical cancer cases averted from the fraction of cervical cancers that have been associated with types 16 and 18? On one hand, given the high proportion of women experiencing multiple infections with oncogenic HPV types, it is likely that many will be affected (although later in life) by one of the remaining (non-16/18) HPV types. On the other hand, the efficacy of the vaccine might be higher than expected, given that there are indications for cross-protection. Given the variety of results above, uncertainty remains: most likely, the true efficacy lies somewhere between 16.9% and 70%.

Apparently, for some, this story is too long to be told. The European manufacturer of Gardasil, Sanofi-Pasteur MSD, when presenting the results of the FUTURE studies, simply claimed "…up to 100% protection against cervical cancer and other HPV-related diseases".[10] More disturbingly, even the German Standing Vaccination Committee (STIKO) assumed a lifelong protection of 92.5%.[11]

What are the downsides of ignoring the uncertainties related to surrogates? Most obviously, decisions at the health policy level as well as the individual level might be misled. Thus, the flawed estimate of the protective efficacy by STIKO influenced the decision to reimburse HPV vaccination in Germany, and probably led many physicians to recommend the vaccination under false assumptions. Second, such data will be inserted into models uncritically: a review found that all cost-effectiveness studies on HPV vaccination at that time had invariably assumed a reduction of cervical cancer cases by 70%.[12] Third, heterogeneity between different age groups can be overlooked: many countries issue recommendations for girls up to 17 years and assume the effectiveness to be 70% for the whole age span below. This is especially puzzling as the result from a surrogate population (women naïve to HPV infection) is applied to a group for which direct study results are available from the FUTURE studies — the 15+ year olds. Fourth, we are unprepared when new research data appear. Recent data on the efficacy of the vaccine Cervarix differ markedly from data on Gardasil.[13] Is this due to differing populations, different surrogates, or does it reflect a higher efficacy? Finally, at least in Germany, the resulting (but unwarranted) confidence in the new vaccines led to the impression that there was no need to actually evaluate their effectiveness.

Epidemiology is about dealing with uncertainties appropriately. Not communicating uncertainties may make a story shorter — but at what cost?

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