Letters to the Editor

THE AUTHORS REPLY

We thank Drs. Basu and Galvani for their observations (1) on our paper (2). However, we disagree with several of their comments. We did not assert that our multiparameter likelihood-based approach was superior to alternative calibration techniques, including Bayesian approaches. Rather, we emphasized the lack of consensus on an ideal approach, credited the “theoretical appeal” of Bayesian methods, and discussed the limitations of our own methods. We suggested that our approach would “appeal to epidemiologists” because of the empirical value of using the full complement of data from a credible cohort study to demonstrate the validity of the model. Van de Velde et al. (3) recently published an elegant analysis of parameter uncertainty in a model of vaccine effectiveness, based on similar principles.

We noted in our paper (2) that Bayesian techniques require “meaningful” prior distributions (not “informative” priors, as
Basu and Galvani mistakenly claim), to highlight the uncontested view that priors are a critical component of Bayesian methods (4). Indeed, uninformed priors may be “meaningful,” since they can reflect the uncertainty of knowledge at baseline. Basu and Galvani state that our approach “is not capable of discriminating among ‘good-fitting’ parameter sets” (1, p. 983). While we agree that a Bayesian approach can offer “specific criteria... for distinguishing among alternative model structures,” we believe that in view of the biologic complexity of the natural history of human papillomavirus (HPV) infection and cervical cancer, capturing the uncertainty, as we did, is more important than using statistical constructs to discriminate among alternative model specifications.

Regarding our finding that natural immunity for high-risk types of HPV generally exceeded 50 percent among good-fitting parameter sets (2), Basu and Galvani conclude—surprisingly—that this indicates “a basic underlying problem with the model” (1, p. 983). On the contrary, we argue that by focusing on the multidimensional space of uncertainty among parameter sets, we revealed the influence of a credible biologic effect that is coherent with the immunologic evidence. In fact, natural immunity is unequivocally an important factor in the host-parasite relation that has evolved over millennia in our coexistence with HPV infection. Naturally occurring antibodies do play a protective role (see reference 61 in our paper (2)); therefore, an estimate of 50 percent is quite compatible with biologic evidence. Our baseline model represented average effects from extensive analysis of the literature, but only through fitting to a particular study could specific sources of variation, such as the one above, be learned.

Finally, as to the suggestion that our model “violates principles of identifiability,” we reiterate the emphasis we placed on capturing the uncertainty that exists in measuring complex biologic processes. As is addressed in the context of other simulation models, when using a “method of acceptance sampling, non- or poor identifiability is less of a problem as we can identify sets of feasible solutions in the high-dimension parameter space” (5, p. 45). Furthermore, the alternative also involves a trade-off: Using more simplistic models for the sake of identifiability may compromise a model’s biologic plausibility and face validity.

All too often we quickly reject alternative methods, which borrow from different disciplines and form innovative approaches to address important questions in the face of methodological challenges. We accept that from the singular standpoint of pure mathematics, there are inevitable methodological limitations to the choices we made; however, we also challenge the authors’ claim that a full Bayesian approach is simple and routine. With the complexity of our model structure, the intricacies of the policy questions being evaluated, and the need for timely analyses, the practicalities of different parameterization approaches were balanced with the end-goal of the modeling exercise. The motivation for our model development efforts resides within a decision analytic framework, with the explicit purpose of informing decisions facing stakeholders today using the data available now, and with the expectation that as better data become available, analyses will be repeated and assumptions revisited.

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REFERENCES

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