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 uncontro-
tested 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 biologi-
complexy 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 prob-
lem 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 evi-
dence. 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 prin-
ciples of identifiability,” we reiterate the emphasis we placed
on capturing the uncertainty that exists in measuring com-
plex biologic processes. As is addressed in the context of
other simulation models, when using a “method of accep-
tance sampling, non- or poor identifiability is less of a prob-
lem 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 simplis-
tic 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 ap-
proaches to address important questions in the face of meth-
odological challenges. We accept that from the singular
standpoint of pure mathematics, there are inevitable meth-
odological limitations to the choices we made; however, we
also challenge the authors’ claim that a full Bayesian ap-
proach 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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