Reply to Cost-Effectiveness Calculations of Human Papillomavirus Vaccination in Punjab May Be Flawed

In their letter, Suman and Puliyel question the validity of our findings[1] on the basis of 3 main points. The first point is based on purported differences between our findings and those of Diaz et al.[2] Diaz et al stated that when the cost per vaccinated girl reached Int $ 20 (US $6.60), the strategy of vaccination alone became dominated by the strategy of screening alone. This point, however, is based on a misinterpretation of our respective findings. Although we compare vaccination with no vaccination, the results cited from Diaz et al's work refer to a comparison of vaccination and screening. The figures that they cite are based, therefore, on a completely different comparison.[3] In fact, in another article,[4] the same group of researchers explicitly compare the choice of human papillomavirus (HPV) vaccination and no vaccination for 72 countries (including India), and they report the following: "Only if the price of vaccine is considered as high as US$ 100 per dose, the cost per DALY averted generally exceeds cost-effectiveness thresholds of the respective countries." Therefore, the findings of our analysis are fundamentally in line with those of Diaz et al.

Second, Suman and Puliyel question the extrapolation of mortality more than 5 years after the initial diagnosis of cervical cancer. The majority of clinical studies report 5-year survival rates for cervical cancer, whereas a lifetime study horizon is the recommended norm for economic evaluations to include all relevant future costs and consequences. In the absence of long-term or life-term consequence data, Tremblay et al[5] provided guidelines for modeling future survival, which are also recommended under National Institute for Health and Care Excellence guidelines. Using an exponential distribution in our study, we used the same methodology to extrapolate future mortality. To model all-cause mortality, age-specific all-cause mortality rates for the female population in Punjab were used from the standard life tables provided by the Sample Registration Survey.[6] In terms of population-level effects on the reduction of cancer mortality due to HPV vaccination, although Goldie et al[4] and the Papillomavirus Rapid Interface for Modelling and Economics (PRIME) model[7] reported reductions of 15 and 8.06 deaths, respectively, per 1000 girls vaccinated, we estimated a reduction of 3.5 deaths per 1000 girls vaccinated, which is much more conservative.

Several sensitivity analyses, incorporating different methodological assumptions and worst case scenarios, were undertaken, and they reinforced the robustness of our findings. First, the incremental cost-effectiveness ratio was robust to the choice of distribution (exponential, Weibull, or Gompertz) used to extrapolate mortality more than 5 years after the diagnosis. Second, we used the estimates of 10- and 15-year survival outcomes reported in a study from Mumbai,[8] and we assumed no further mortality beyond 15 years. In such a case, HPV vaccination incurs an incremental cost of 80 Indian rupees (95% confidence interval, 49-123 Indian rupees) per quality-adjusted life-year gained. Third, we incorporated a worst case scenario, in which we assumed no deaths among the survivors of cervical cancer beyond those reported at 5 years and, therefore, no benefit in mortality reduction after 5 years. In this scenario, HPV vaccination would cost 19,725 Indian rupees (95% confidence interval, 8192-45,580 Indian rupees) per quality-adjusted life-year gained with a 90% probability of being cost-effective at a willingness-to-pay threshold of 20,000 Indian rupees, which is well below the cost-effectiveness threshold of the gross domestic product per capita (India's gross domestic product per capita in 2016 was 112,800 Indian rupees).[9,10] Hence, the overall conclusion regarding the cost-effectiveness of HPV vaccination is robust; furthermore, HPV vaccination remains cost-effective even if we make the most extreme conservative assumption of no impact on mortality after 5 years.

Third, Suman and Puliyel have incorrectly calculated the life-years gained per death averted. The model estimates the life-years lived by both those who are diseased and those who are not diseased as well as those who die a natural death. Once these are adjusted, our model estimates 20.2 life-years gained per death averted. Although disaggregated figures in terms of health gains have not been reported in most similar studies, we tried to compare the findings of our analysis with those who have reported them. HPV vaccination saved 9 quality-adjusted life-days per person in Thailand[11]; this figure is 32 according to our study. That more quality-adjusted life-years are gained from HPV vaccination in India is justifiable for 3 reasons. First, 90% of cases in Thailand are diagnosed at stage 2 or earlier, whereas 51.6% of cases in India are detected at stage 3 or 4 when the survival prognosis is quite adverse.[12] Second, the survival rates reported in the

Thai study for each stage are on average 15% to 40% higher than the rates reported in Indian settings and hence used in our analysis.[11] Finally, because detection occurs for the majority of women at late stages, which are associated with a much worse quality of life, preventing cervical cancer due to HPV results in greater gains in quality-adjusted life-year terms.

Hence, we disagree with Suman and Puliyel: our findings of cost-effectiveness for HPV vaccination are valid and should be used for policy in India.

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