ISSN: 2278-330X

SAJC

South Asian Journal of Cancer

Volume 3 • Issue 1 • January-March 2014

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Authors' Reply

Dear Editor,

We appreciate Dr. Palefsky's interest[1] in our recent article[2] on the suitability of mass human papilloma virus (HPV) vaccination in India and similar countries. Much of the opinion expressed in his letter is based on biased interpretation of data and inconsiderate dismissal of facts and logic.

His contention that intent-to-treat populations are irrelevant in randomized HPV vaccine trials is contrary to all tenets of data interpretation and strikes at the very basis of intention to treat principle. For example, the mean age of women enrolled in one of the randomized trials[3] was 20 years. Are "girls before they initiate sexual activity" likely to follow this demographic? Another, very topical example, is the recent report that the black population in US may be significantly less protected by the currently available bivalent and quadrivalent vaccines.[4] Yet another very recently published report studied the effectiveness of quadrivalent vaccine using population-based individual level data sourced from administrative health databases in the Canadian province of Manitoba.[5] This study showed that a considerable fraction of vaccinated women may not be protected against cervical dysplasia. These fact would be of no interest to observers, like Dr. Palefsky, who believe that per-protocol analyses of the published trials have proven everything that needed to be proved about HPV vaccination, in all populations. The convenient extrapolation of "per-protocol" data to women who differ significantly from this population and ad hoc dismissal of intent-to-treat groups, which show considerably less efficacy, is meant to sweep very uncomfortable facts under the carpet.

The fact that cervical cancer rates have declined over the past several decades and continue to decline has been extensively documented in several population-based Indian cancer registries and there is no reason to believe that this decline will suddenly halt, despite the wishful thoughts of vaccine advocates.[6] As testimony, for the very first time, cervical cancer incidence and mortality have fallen behind that of breast cancer for the whole of India.[7] It is also a matter of well-documented fact that this decline has occurred without systematic screening or mass vaccination. One can only imagine a situation where vaccination had been introduced several decades ago and the decline conveniently attributed to this intervention. Cervical carcinogenesis (as indeed most cancers' origins) is a complex multifactorial process involving several host and environmental factors – HPV is but one part of the jigsaw. Failure to appreciate this fact (or its deliberate obfuscation) lies at the heart of vaccine advocates' inability to accept that dynamics other than HPV vaccination can consistently reduce the incidence of this disease.

The fact that cervical cancer is a very rare outcome of HPV infection is absolutely germane to this discussion – the consequent (vaccinated) number needed to prevent one cervical cancer death is enormously high, assuming, of course, that vaccination will indeed prevent that outcome. Dr. Palefsky points out that there is proof of continuing protection against infection by one HPV subtype (HPV 18) in 8-year follow up data. He implicitly agrees with our statement that the real duration of protection is unknown, including against all subtypes of interest. Here it would pertinent to point out that the actual duration of interest is several decades, when a 12-year-old female is sought to be vaccinated and protected over a considerable fraction of her lifetime.

Dr. Palefsky has dismissed offhand several key safety concerns associated with HPV vaccination including the possibility that carcinogenesis could be accelerated if already infected women are vaccinated. There is no easy way to find out the infection status of an intended vaccine recipient in a mass vaccination campaign. The ATHENA study[8] reported the results of a large cervical cancer screening trial, enrolling 47,208 women 21 years of age or older at 61 clinical sites throughout the United States. In women between 21 and 29 years, the absolute reduction in prevalence of HPV 16/18 in vaccinated (8.1%) compared to unvaccinated group (8.7%) was 0.6%. This was outstripped by a 5.1% increase in prevalence of other high risk HPV types (not covered by available vaccines) in vaccinated (30.8%) compared to unvaccinated women (25.0%). The impact of these and similar findings on cervical cancer incidence, far into the future, is unknown. Further, although the U.S. vaccine adverse event reporting system shares inherent limitations of all passive surveillance systems,

it is national in scope and can provide important signals worthy of further attention. In one report from this system[9] the estimated weekly reporting rate of post-quadrivalent vaccine Guillain-Barré syndrome (GBS) within the first 6 weeks (6.6/10,000,000) was higher than that of the general population and higher than post-meningococcal C vaccine and post-influenza vaccinations. In particular, there was a nearly 2.5-10 times greater risk of acquiring GBS within 6 weeks after quadrivalent vaccination when compared with general population. In addition, quadrivalent vaccination was associated with approximately 8.5 times more emergency department visits, 12.5 times more hospitalizations, 10 times more life-threatening events and 26.5 times more disability than meningococcal C vaccination. Of the 34 patients who developed GBS within 6 weeks post-vaccination, 25 (74%) developed symptoms within the first 2 weeks. The probability of observing an asymmetrical distribution over the 6 weeks by chance alone was low (P = 0.0002). Dr. Palefsky dogmatically states that there are NO (emphasis his) safety concerns by citing the safety surveillance study of Slade *et al*.[10] He cites selectively and conveniently. We quote Slade *et al*. fully from their conclusions (emphasis ours): "Most of the adverse event following immunization rates were not greater than the background rates compared with other vaccines, but there was disproportional reporting of syncope and venous thromboembolic events. The significance of these findings must be tempered with the limitations (possible underreporting) of a passive reporting system." It bears reiteration that the safety standards expected of a primary preventive intervention are extraordinarily high, especially when the claimed benefits are decades away.

We agree with Dr. Palefsky that the current rates of cervical cancer in India (although declining) continue to be high and need intervention. It is indisputable that effective screening will lead to huge reductions in cervical cancer mortality– with far less (screened) number needed to prevent because the endpoint (cervical intraepithelial neoplasias) is considerably more proximate to the eventual outcome of interest (invasive cancer) than is HPV infection. That India has been unable to mount an effective cervical screening program is a monumental public health failure– but not an excuse to mass vaccinate millions of women without adequate proof of effectiveness. In this context, the acetic acid screening trial recently presented by our Center proved a highly significant reduction in cervical cancer mortality with proof that it could be implemented at the community level.[11] This program is currently being adopted by several State Health Departments in this country.

It is possible that mass HPV vaccination may be proven (or refuted) to be an effective strategy for reduction in population cervical cancer mortality rates, at some point of time in the future. However, its utility as a public health measure, on the balance between claimed benefits, possible harms and cost, remains unproven at present. We remain of the considered opinion that health policy planners in India would be well advised to carefully assimilate independent opinion on this subject that is not influenced by vaccine manufacturers, who stand to gain enormously from implementation of this intervention in vast populations. We also strongly advocate the immediate implementation of a cervical cancer screening program in this country that is feasible and cost-effective.

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