

## References

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DOI: 10.1258/jrsm.2012.120207

## Should the ideal be the enemy of the good?

In Mattheij *et al.*<sup>1</sup>, the authors claim that HPV vaccine is not warranted in India due to supposedly low rates of cervical cancer and poor data. While we agree that the quality of registry data on cancer is far from ideal, that is true for many global health problems (including diabetes, which has no disease registry at all). Fortunately, lack of registries has not prevented governments from tackling pressing health problems.

We believe the authors have misinterpreted the Indian registry data. For

example, they do not acknowledge that the decline in rates was an urban phenomenon, and that it was not reflected in the one rural registry (Barshi)<sup>2</sup>. To understand disease burden PATH relied upon the WHO's GLOBOCAN database<sup>3</sup>, which estimates that India has the highest absolute number of cervical cancer cases in the world.

The study sites in Andhra Pradesh and Gujarat were selected in consultation with a national project advisory committee and were based on multiple criteria, not only regional disease incidence; these included immunization coverage, experience with new vaccine introduction, and commitment to adolescent health and cervical cancer prevention<sup>4</sup>.

The authors cite the WHO document on new vaccine introduction<sup>5</sup> as requiring that disease burden data and national surveillance be in place before any new vaccine can be used. While these guidelines set out a worthy ideal to strive for, they did not hold up the introduction of polio or measles vaccines, neither of which has the kind of comprehensive surveillance system the authors call for.

Finally, the study was not an effort to introduce or rollout HPV vaccine either nationally or in the two Indian states. Its purpose was to generate evidence on feasible, acceptable, and affordable strategies for delivering the vaccines, should the Indian government decide one day that such a service belongs in their cervical cancer control program. Should that day come, the data generated by the HPV vaccine study will prove useful to immunization planners.

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### Competing interests

None declared

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DOI: 10.1258/jrsm.2012.120201

## Author's Response: HPV vaccination in India

Babu makes the important point that cervical cancer estimates are not representative of the country as a whole as they draw on data derived from registries which cover around 5% of the population who are mainly living in urban areas.<sup>1</sup> This is a major problem for their use in policy making. It is important to point out that contrary to Babu's claims our study was not designed to look at causality, rather it took a critical look at the comprehensiveness, quality and coverage of cervical cancer data collected by Indian registries supplementing it with a lit search of epidemiological studies of cancer incidence and human papillomavirus (HPV) type prevalence. Our aim was to establish whether there was high-quality public health evidence to support the claims made by PATH in justifying the conduct of the HPV trials in India and whether in line with World Health Organization criteria there is effective surveillance to support the role out of HPV vaccination.

GLOBOCAN draws on data from eight randomly selected cancer registries which do not represent all regions of India equally, but mainly central and southern areas.<sup>1</sup> The large differences in incidence and mortality rates between and within states reported by registries indicate difficulties in extrapolating such data to the whole of the population.<sup>2</sup> The Lancet paper cited by Forman *et al.* reporting on mortality rates is highly problematic

for a number of reasons.<sup>3</sup> It is based on a sample survey of all deaths in a million homes undertaken between 2001 and 2003 using verbal autopsies. The study itself generated very small numbers on cervical cancer deaths overall. A total of 391 deaths were classified as cervical cancer for both rural and urban populations together and there was agreement between the two coders for 324 cases. Moreover, there were problems over quality and accuracy of data, and a sensitivity analysis was not performed. These relatively small numbers of deaths were then extrapolated to the whole population of India and projected forward to 2010, which in itself is problematic because of changing cancer patterns and lack of generalizability to the population.

The authors agree with our interpretation of data that shows cervical cancer incidence declining over time in some urban regions.<sup>1,4,5</sup> They attribute this decrease to family planning, education and socioeconomic improvement combined with programmes for screening and early detection. In the absence of high-quality comprehensive cancer surveillance it is not possible to test these claims nor to justify the implementation of human papillomavirus (HPV) vaccination programmes on public health grounds. The high-quality work of the NCRP cancer registries in India should be expanded.

An increasing number of studies in the last few years indicate that HPV 16 and HPV 18 are most commonly associated with cervical cancer across different areas in India. It should be noted that notwithstanding the claim that cervical cancer is one of the leading causes of cancers in India among women, its importance diminishes against other causes of

mortality for women and moreover cervical cancer rates appear to be declining.

Our paper shows that World Health Organization criteria with respect to monitoring effectiveness of the vaccine and knowledge of disease trends cannot be fulfilled because there is as yet neither comprehensive cancer surveillance nor is there a universal health system in India. The Indian government, in our view, is correct in not prioritizing HPV vaccination as a public health intervention for the population.

There are several flaws in the response from PATH. Crucially, PATH does not address the core issues of HPV vaccine efficacy and its costs. It is wrong to compare the vaccine with polio and measles where efficacy was known. Whether HPV vaccine will reduce cervical cancer incidence and mortality rates is completely unknown and yet HPV vaccine is being promoted, promulgated and sold worldwide in the absence of absolute proof of principle, relying on proxy endpoints. At the same time, information about the evidence underpinning the decision making process is unpublished and not in the public domain. PATH has put the cart before the horse. Why conduct safety and feasibility studies if efficacy and indications for the vaccine are unknown.<sup>1</sup>

PATH state that they rely on GLOBOCAN data and claim that rural populations have a higher incidence. Our analysis shows that GLOBOCAN and other data have important gaps and that Indian registries underrepresent the rural population and exclude many regions of India.<sup>2</sup> Without a proper surveillance system and healthcare system we will not know whether there is a need for a vaccine or whether the vaccine works.

The opportunity costs of rolling out a vaccine trial where the efficacy of HPV is unproven has serious consequences for public health budgets and the household expenditure of the poor. Regrettably, HPV vaccine is already being promoted and sold to women and girls in India.

The authors assert that India has the highest absolute number of cervical cancer cases a claim that could be made for most diseases by virtue of India's population size. The same claim is equally true for the number of people without proper sanitation, access to primary care etc. The government must consider the overall healthcare and health service needs of the population.

For all these reasons the Indian government is quite correct not to prioritize HPV vaccination as a public health priority.

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#### *Competing Interests*

None declared

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DOI: 10.1258/jrsm.2012.12k066

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