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# Reply to S D Rathod's Commentary on HPV screening for cervical cancer in rural India

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The study in Osmanabad district, India (1), was organised to measure the effect of a single round of screening by HPV testing, or quality assured cytology, or visual inspection with acetic acid (VIA) on cervical cancer incidence and mortality, whereas reductions in disease have followed repeated rounds of high-intensity screening in developed countries. Prior to this study there was only evidence from model-based studies that a single round of screening may lead to significant reductions in disease burden. Thus, in contrast to the impression given by Rathod (2), this study was not a repeat of work conducted in developed countries but was unique in addressing the impact of a single round screening with different tests, with a research question and study design directly relevant to developing countries. It is crucial that this type of high-quality research is encouraged in order to inform public health decisions in regions where health services face difficult challenges.

The study was designed as a cluster randomised trial to avoid contamination between the study groups and for logistic convenience. We decided that providing services to clusters of women with a given screening test is more convenient in terms of clinic organisation than providing different screening tests in the same village clinic for a group of women based on individual randomisation. Moreover, it prevents any possible unintended error in providing appropriate screening test as per randomisation and women crossing over to different interventions at random.

The standard of care for cervical cancer control in India is clinical diagnosis and treatment of invasive cancer only when symptomatic women seek medical attention. There is no organised or large-scale opportunistic cervical cancer screening programme anywhere in the country. Around one million cervical smears are taken annually in a sporadic fashion, mostly in urban areas, in a country where there are more than 150 million women in the age group 30 to 59 years. For instance, only 8 of the 131,746 women aged between 30 and 60 years in our study population had ever had a Pap smear, indicating the scarcity of routine screening in the general population.

Whenever a new intervention is evaluated, it is compared with the standard of care existing in the country. It is important to know if a single round of screening has the ability to reduce disease burden significantly, over and above the existing care, before taking decisions on implementing them as a public health policy, particularly in poorly financed health services. Thus the control group in our study was not offered screening, but they were educated on a person to person basis on cervical cancer, its risk factors, symptoms and signs, its prevention, early detection, treatment and where to seek cytology and follow-up services, by the study health workers who interviewed them for socio-demographic factors. Probably due to the education received, 1,946 (6.2%) women in our control group sought Pap smear and among those 15 were detected with histologically proved high-grade disease, 41 were diagnosed with invasive cancer, and all were offered appropriate treatment.

The study was adequately powered to address the research question that we set out to answer and to detect a clinically relevant effect for India and other low-resource countries, as described in the manuscript. The death rate from cervical cancer in women aged 30 to 59 years was assumed to be around 20 per 100,000 women and the actual death rate in the control group was 25.8 per 100,000 person years.

Evidence on disease burden in terms of incidence and mortality, particularly from randomised controlled trials, provide the most persuasive evidence for the effectiveness of a novel screening approach, such as a single round of screening, rather than results of the accuracy, detection rates of precancerous lesions and model-based studies of screening tests which are unlikely to drive public health policy changes on their own.

Informed consent in studies in developing countries may be portrayed as contentious by researchers who have limited understanding of the prevailing socio-cultural context. In our study, the health workers read out the consent form in the local language, explained the interventions, responded to the participants' doubts and questions, and enrolled women who were willing to participate. There was no coercion whatsoever. It would be unfortunate to imply either that people in developing countries are unable to comprehend the risks and benefits of interventions provided to them simply because they have less formal education, or that researchers in developing countries administer the informed consent process in an ambiguous or incomplete manner. Furthermore, it is presumptuous to think rural women with no formal education are incapable of understanding and comprehending what is being offered to them and making a decision to participate or not or to withdraw from the study at any given time during its course.

The study was planned, conceived and implemented by a group of experienced investigators in India and abroad, who are well versed in the prevailing socio-cultural norms and health services in rural India. Particular care was taken to provide the entire continuum of services comprising education, accessible screening clinics, provision of quality assured screening tests by trained providers, diagnosis, treatment and follow-up care of screen-positive women and effective information systems to monitor and evaluate the inputs and outcome as diligently and efficiently as possible. It is rather surprising to suggest that the project was implemented sub-optimally because certain interventions did not show mortality reductions in this study context. It is not surprising to find studies with contrasting findings. In addition, we have not precluded the possibility of under-diagnosis and underestimation of invasive cancer cases in the control group due to a relatively underdeveloped routine cancer health services in the region and a proportion of symptomatic cases not seeking diagnostic and treatment services (3). Perhaps this might be a reason for the lack of incidence effect in the study for all the arms and for the lack of mortality effects in the VIA and cytology arms. Alternatively, a single cytological screen or VIA screen might not have been consistently sensitive for detecting biologically significant high-grade precursors with the potential to progress to invasive cancer, due to the provider-dependent subjective nature of these tests. If this is true, repeated rounds of cytology may be necessary to reduce cervical cancer burden.

The high level of participation of the target population in screening, diagnosis, treatment and follow-up over several years in our study is an excellent testimony to the comprehension of the community, the general public, the women and their families, as well as the municipal and civic authorities in the study location. Their much appreciated cooperation in the successful conduct of this original piece of research allowed a crucial public health problem for many developing countries across the world to be addressed.

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