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DISCUSSION

Response to an article titled “US-funded measurements of cervical cancer death rates in India: scientific and ethical concerns” by Eric Suba, published online on April 17, 2014 in the *Indian Journal of Medical Ethics*

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Dr Eric Suba has been distorting facts and persistently disseminating biased and misleading views and statements regarding our studies over the past several years. His article in the *Indian Journal of Medical Ethics* (1) fails to mention the facts that seem unfavourable to his arguments, and the ethical concerns are unsubstantiated by the evidence. In this context, we present the following clarifications for the attention of your readers, notably with regard to: (i) the study design and inclusion of a control group; (ii) the informed consent of the women participating in the study; (iii) the conformity with international ethical standards and guidelines, and (iv) the provision of screening to women in the

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control arm of the studies. We also highlight the benefits that are flowing from this research and the risk that misinformation may further delay access for women to life-saving cervical cancer screening.

The aim of our studies (2, 3) was to provide an affordable, feasible, effective, and evidence-based way of preventing cervical cancer in low- and middle-income countries. Repeated rounds of cytology-based cervical screening at 3- or 5-year intervals as in high-income Western countries, is not feasible in countries such as India given the level of resources required. Such approaches to cervical screening in middle-income Latin American countries over the past three or four decades have not contributed to reductions in the incidence of cervical cancer due to the striking deficiencies in: provision of quality-assured cytology screening tests in the frequently repeated screening rounds, participation of women eligible for screening and treatment, and lack of proper monitoring and evaluation during the roll-out of these programmes (4). Taking these limitations into account and the findings from model-based studies, a single life-time screening is an alternative paradigm for cervical screening because of low costs and the likelihood of high participation in a single round.

When we organised the studies in 2000, we had no evidence whether a single round of screening would be effective in reducing the number of cases of cervical cancer or deaths due to cervical cancer compared to the existing care. Thus, rigorous evaluation of its efficacy in well-designed and conducted studies was crucial before evolving a public health policy at the population level. Our motivation was to evaluate this approach.

In designing the study, we applied the principle that whenever a new intervention is evaluated, it is compared to the standard care existing in the country and only subsequently should it be implemented as a public health policy. Therefore, our study involved a control group which received routine care plus education on prevention of cervical cancer and early detection by screening as well as advice on how and where to seek screening, early diagnosis and treatment services. At the time the studies were conducted, the standard care for control of cervical cancer in India was health education, diagnosis, and treatment among symptomatic women when they sought medical attention; there was no screening programme anywhere in India. The World Health Organisation (WHO) was advocating just health education in places where screening was not affordable or feasible (5). The fact that population-based cytology screening is not feasible in India is not our invention; it has been determined by the Indian Council of Medical Research (ICMR) in 1992 (6) and again in 2006 by a joint WHO–Government of India Guideline Committee (7). As per the Helsinki Declaration guidelines, updated as of 2013, where no proven intervention exists, the use of placebo, or no intervention is acceptable (8). The studies referred to by Dr Suba (2,3,9) have been conducted entirely in India, initiated by competent, ethically and socially conscious Indian investigators to find solutions for India and other low- and middle-income countries, which are not *a priori* going to be synonymous with those in North America or Europe.

Contrary to Eric Suba's claim, the Indian National Cancer Control Programme in 1985 clearly stated that cervical cytology screening programmes were not feasible, given the level of resources and cytology infrastructure available, and that early clinical diagnosis and treatment of invasive cancer among symptomatic women was the chosen policy to control cervical cancer in India (10). In fact, of the 131,806 eligible women in the Osmanabad district study, only 8 had ever undergone cytology

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screening before the study was undertaken, exemplifying the lack of cytology screening at that time (2). Even now, almost 30 years later, only two states (Sikkim and Tamil Nadu) among the 30 states in India offer screening and chose visual inspection with acetic acid (VIA) since 2008 in a programme mode through routine public health services based on the results of our Dindigul study (3) and other VIA studies in India. This choice to use VIA was made as widespread cytology screening is simply not feasible. Eric Suba states that "Papanicolaou screening is feasible anywhere that cervical screening is appropriate" which indicates that he has little understanding about the prevailing conditions in many low- and middle-income countries in sub-Saharan Africa, Central America, and South Asia.

In relation to informed consent, our studies were explained in the local language to all eligible women and written informed consent was obtained from each participant. As experienced Indian scientists and clinicians, we find it misleading when someone implies that Indian women do not have the common sense and intelligence to understand and comprehend the study procedures, interventions, harms, and benefits in order to make an informed decision to consent to participation. It has become routine in some quarters to question the informed consent processes and ethics of studies in developing countries and the scientific capability and integrity of investigators from these countries, without understanding the prevailing sociocultural norms and the level of development of health services.

Moreover, Dr Suba seems to imply that all three Indian trials were subjected to inquiry by the US Office for Human Research Protections (OHRP). Whereas the truth is that the OHRP determinations are applicable to only one of the three studies (9), and even these determinations are contorted by Dr Suba to misguide readers. We would like to place on record that the OHRP, after due inquiry, have determined through their letters dated January 13, 2013 and July 13, 2013 that the corrective actions taken by the Tata Memorial Hospital Institutional Review Board (TMH IRB) adequately address the earlier determination of non-compliance. These letters of determination, which Dr Suba has avoided mentioning, are available in the public domain on the OHRP web site (11, 12).

The study proposals and procedures were developed following substantial consultation with experts from India and abroad. The study proposal was reviewed and approved by the institutional review boards and ethics committees of the Tata Memorial Hospital (TMH), Mumbai for the Osmanabad district study (2) and the Christian Fellowship Community Health Centre (CFCHC), Ambillikai, for the Dindigul district study (3) and the International Agency for Research on Cancer (IARC) of the WHO, Lyon, for both studies. The studies were implemented by competent investigators and staff from the TMH, Mumbai (PIs: [Late] Dr K Dinshaw and Dr Surendra Shastri), which is the premier cancer hospital in India and the Nargis Dutt Memorial Cancer Hospital (NDMCH), Barshi (PIs: Dr BM Nene and Mrs K Jayant), and the CFCHC, Ambillikai (PIs: Dr R Rajkumar and Dr P Esmay) with the registration of cancer cases in Dindigul district carried out by the Dindigul Ambillikai Population-based cancer registry (PI: Dr R Swaminathan) run by the Cancer Institute, Chennai.

Cervical cancer screening services were provided in the villages of the intervention arms whereas the participants in the routine care control group were educated about cervical cancer signs and symptoms, early detection and prevention and where to seek cervical screening services; they were also encouraged to seek cervical screening, early diagnosis and treatment from healthcare facilities.

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Patients clinically diagnosed with cervical cancer in the control group received free treatment and none were denied diagnosis and/or treatment. In addition, 1956 women from the control group in the Osmanabad study (2) sought screening at the NDMCH and were tested with Pap smear and treated adequately and 553 women of the control group in the Dindigul study (3) sought VIA screening at the CFCHC during 2000–2003. From the outset, we also committed that if one particular screening method proved effective in the study, we would provide the same to the control group before closing down the study.

The studies were closely monitored and evaluated during their progression by the investigators at TMH, NDMCH, CFCHC and the Cancer Institute, Chennai. Progress was also regularly reviewed by the IARC Scientific Council and internal reviews at the Indian institutions. The results after 9 years of follow-up in the Osmanabad district study (2) indicated that a single round of HPV screening was associated with a significant reduction in advanced cervical cancers and deaths from cervical cancer. The results of 7 years of follow-up in the Dindigul study showed 25% and 35% reductions in cervical cancer incidence and mortality, respectively following VIA screening (3) and the feasibility, safety, and efficacy of a single-visit screen-and-treat approach (13).

Our research findings have been appreciated worldwide and have contributed to further advances in cervical cancer prevention globally. They are among the highest impact scientific studies in medicine not only from India, but also from the entire low- and middle-income countries. The work was published in medical journals of high repute such as the *New England Journal of Medicine* (2) and the *Lancet* (3) after rigorous peer review. An editorial entitled “From India to the World—a better way to prevent cervical cancer” in the *New England Journal of Medicine* commented that the implications of the findings of the Osmanabad district study are immediate and global and international experts in cervical cancer prevention should now adapt HPV testing for widespread implementation (14).

As per our initial commitment, we have provided HPV testing for the control group subjects in the Osmanabad district study using HPV testing, and VIA screening to the control group in the Dindigul district study after the publication of the results. Contrary to other randomized controlled cancer screening trials across the world, screening the control group after results were published was only made possible thanks to the generous support from the Bill and Melinda Gates Foundation through the Alliance for Cervical Cancer Prevention (ACCP). We have also provided VIA screening to the women in the remaining areas of Dindigul district, outside the context of the research project. As a consequence, the incidence rates of cervical cancer in the district have substantially declined in recent years (15). Following the significant reduction in the rates of incidence and mortality of cervical cancer in our study, the Tamil Nadu Government has been scaling-up VIA screening through the existing health services to cover the entire state in a phased manner since 2007, thereby rapidly bridging the demonstration of effectiveness in a locally conducted randomized trial and implementation in everyday healthcare (16).

It is mischievous to highlight that 254 patients with cervical cancer died in the control groups of the three studies (2,3,9), but omit to mention that 208 patients with cervical cancer in the screened groups died of cervical cancer. Unfortunately, this has led to sensational news headlines in the lay press, which misleadingly imply that 254 women died in the studies for want of care or due to a lack

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of treatment. It is not possible to cure every cervical cancer patient with treatment, particularly those with advanced disease. However, as the studies showed, more deaths can be avoided by the early detection and treatment of disease through a single-visit screen-and-treat approach. Contrary to the distortion used to imply that participants died because of lack of treatment, all patients in the intervention and control groups reporting to the CFCHC or NDMCH were provided standard treatment as per the institutional policies stage for stage free of cost (2,3). The treatments used in the studies including field-based treatments for precancerous lesions proved safe and there were no significant adverse events associated with screening tests and the treatment of precancerous lesions (13,17,18). In fact, our studies contributed to more widespread use of cryotherapy and loop electrosurgical excision procedures for the treatment of precancerous lesions which were practically non-existent or very limited in many states of India.

It is malicious on the part of Dr Suba to imply financial conflicts of interest between us and the manufacturer of the HPV test: this is contrary to the truth. We purchased the product and the industry neither supported the study with any funding nor had any role in its design, conduct, data analysis, or reporting of results and had no association with the study or its investigators.

We reiterate that our studies conducted in India by Indian scientists and clinicians are of the highest order of scientific and ethical merit and we completely refute the said allegations. It is rather strange that Dr Suba questions the scientific validity of our Osmanabad study (2) in his *IJME* article (1) while he quotes the same study to support his statement that Indian women screened with HPV testing had better health outcomes compared to those screened with cytology in a 2011 communication published by him in the *Journal of the National Cancer Institute* (19). His repeated criticism and inconsistent and selective presentation of the facts must not be allowed to further delay access to the best possible cervical cancer prevention and treatment for women in some of the poorest countries in the world: that would be unethical.

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