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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Response by Eric Suba to Sankaranarayanan et al

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During the 1970s and 1980s, reports from several countries documented substantial reductions in incidence rates of cervical cancer and death rates following the introduction of cervical screening and confirmed the role of cervical screening as an archetypal preventive health intervention; moreover, reductions in death rates due to cervical cancer were directly related to levels of screening (1). In 1997, Sankaranarayanan accurately observed that "even screening women once in a life-time at an appropriate age in low-resource countries may reduce the incidence of cervical cancer by 30%" (2). It is astonishing that Sankaranarayanan et al would subsequently characterise cervical screening as a "new intervention" and claim that "when we organised the studies in 2000, we had no evidence whether a single round of screening would be effective in reducing cervical cancer cases or cervical cancer deaths as compared to the existing care" (ie no screening whatsoever). The study in Mumbai, which was organised in 1997 and funded by the US National Cancer Institute (NCI),

compared four rounds of cervical screening to no screening whatsoever. Logically, Sankaranarayanan et al would also have to claim that they had no evidence in 1997 whether four rounds of screening would be more effective in reducing death rates due to cervical cancer, compared to no screening whatsoever. Such claims appear to be understandable exercises in self-preserving denial. If Sankaranarayanan et al were to acknowledge now that they knew, when they organised these studies, that some cervical screening was better than no screening whatsoever, then they would be admitting to egregious professional misconduct.

Sankaranarayanan et al declare that "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 is precisely because Indian women are fully capable of understanding such information that these US-funded studies required inadequate informed consent. If, at any time during the past 15+ years, the 138,624 Indian women in unscreened control groups had been told the simple truth that "even screening women once in a life-time at an appropriate age in low-resource countries may reduce the incidence of cervical cancer by 30%," these women would have left their control groups and obtained screening on their own. To suggest, as do Sankaranarayanan et al, that Indian women would knowingly consent to be randomly assigned to more death – instead of to more life – is to suggest that Indian women are unimaginably stupid. To enrol and sustain the unscreened control groups in these US-funded studies required withholding critical information from all 363,553 study participants regarding the predictable health benefits of one to four rounds of cervical screening, compared to no screening whatsoever. The US Office for Human Research Protections (OHRP) investigated only the NCI-funded study in Mumbai because OHRP had no authority to investigate the studies in Osmanabad and Dindigul, which were funded by the Bill & Melinda Gates Foundation. The inability of the OHRP to investigate the studies in Osmanabad and Dindigul should not be viewed as an exoneration of those studies. The actions taken by the Tata Memorial Hospital Institutional Review Board to satisfy the cosmetic changes requested by the OHRP do not alter the reality that the defective scientific design of these studies required inadequate informed consent.

Sankaranarayanan et al state "the fact that population-based cytology screening is not feasible in India is not our invention" and "Eric Suba states that 'Papanicolaou screening is feasible anywhere that cervical screening is appropriate' which clearly 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." Not everything that is feasible happens, but everything that happens is feasible. In fact, Sankaranarayanan established the feasibility of population-based cytology screening in India when he began performing it in rural Osmanabad in 1999. Moreover, by 2005, Sankaranarayanan had concluded that "our results clearly show that good-quality cytology can be implemented even in a rural setting of a developing country with reasonable investment" (3).

The extraordinary persistence of Sankaranarayanan's irrational belief in the impossibility of cytology screening in low- and middle-income countries is further exemplified in two publications of 2001. By September 2001, African leaders had concluded that "95% of institutions at all healthcare levels in East, Central, and Southern African countries had the basic infrastructure to carry out cervical cytology screening" (4). It is astonishing that, in November 2001, Sankaranarayanan flatly contradicted the September 2001 conclusion of African leaders, declaring that "many low-income developing countries, including most in sub-Saharan Africa, have neither the resources nor the capacity for their health services to organize and sustain any kind of screening programme" (5). It is profoundly alarming for the health of the world-s women that the World Health Organisation's International Agency for Research on Cancer harbours such immutable yet irrational opposition to cytology screening for precisely those communities in the world that are at highest risk for death from cervical cancer. Unintended negative consequences may result when research professionals are given leadership roles in development efforts.

In the spring of 2014, scientific and ethical concerns regarding these US-funded studies in India were presented at the National Center for Bioethics in Research and Healthcare at Tuskegee University during its annual commemoration of President Clinton's 1997 apology for the iconic Tuskegee Syphilis Study. The gist of the Tuskegee presentation was that, whether in Alabama, Mumbai, Osmanabad, or Tamil Nadu, "you can't let people die to show something you already know" (6). Policy-makers do not require decades-long randomized trials incorporating cervical cancer death-rate measurements among unscreened women in order to learn that cervical screening prevents cervical cancer. Policy-makers can just glance at a book. It is of critical importance for Sankaranarayanan et al to explain what we learned from the deaths of the women in their studies that we did not already know. They have failed to do so. They have also failed to explain why death-rate measurements among unscreened women continued even after mortality benefit from screening had – predictably – been confirmed. If, as appears certain, we predictably learned nothing from the deaths of these women that we did not already know, then these India screening studies may become regarded, together with the Tuskegee Syphilis Study, as among the most scientifically and ethically problematic clinical studies ever supported by US taxpayers.

Given the considerable stakes involved, and given recent disclosures that top US health leaders may have inappropriately interfered with domestic American bioethical investigations (7), the current conversation will greatly benefit from the direct participation of top US health leaders. NCI Director Harold Varmus, whose US taxpayer-supported institution funded the study in Mumbai, should be invited to explain in the *IJME* what

we learned from the deaths of women in Mumbai that we did not already know. Also, Mr Bill and Ms Melinda Gates, whose tax-exempt institution funded the studies in Osmanabad and Dindigul, should be invited to explain in the *IJME* what we learned from the deaths of women in Dindigul and Osmanabad that we did not already know.

As part of these explanations, NCI cervical cancer expert Mark Schiffman, who praised the Osmanabad study in the *New England Journal of Medicine* (8), should be invited to explain whether one of the central findings of the Osmanabad study – that Papanicolaou screening does not prevent cervical cancer – is scientifically valid. If that absurd finding is in fact scientifically invalid, then the incidence-rate and death-rate measurements from the Osmanabad study (and, by implication, from the Mumbai and Dindigul studies as well) are scientifically meaningless. Indeed, the Tamil Nadu government did not suspend VIA screening in that state after the Osmanabad study showed that VIA screening apparently does not prevent cervical cancer, suggesting that Indian policy-makers may consider US-funded cervical cancer incidence-rate and death-rate measurements to be scientifically meaningless. Sankaranarayanan et al have failed to explain why VIA apparently succeeded in preventing cervical cancer in Dindigul when it apparently failed to do so in Osmanabad, or why quality management for VIA failed catastrophically in Mumbai.

As Sankaranarayanan et al note, their "work was published in medical journals of high repute such as the *New England Journal of Medicine* and the *Lancet* after rigorous peer review." Results from the Tuskegee Syphilis Study were also published in some of the world's most prestigious medical journals throughout the 40-year duration of that study. Editors of the *Lancet*, the *New England Journal of Medicine*, the *International Journal of Cancer,* and the *Journal of the National Cancer Institute* should be asked whether their publications of data collected from research subjects whose consent had been improperly obtained are compliant with guidelines for the protection of human research subjects established by the International Committee of Medical Journal Editors. If Sankaranarayanan et al desire the number of cervical cancer deaths in their control groups to be referenced by a number other than 254, they are entitled to specify that number and should do so.

Finally, the allegation by Sankaranarayanan et al that suggestions of financial conflicts of interest are "malicious" is false. I harbour no malice towards Sankaranarayanan et al or towards their American enablers. However, I do acknowledge that I have harboured – for more years than I care to count – an evolving sense of anger in the face of what I have perceived as meaningless, avoidable harm and death visited on desperately vulnerable women in the names of US taxpayer-supported science and philanthropy.

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ERRATA

We apologise for errors in the printing of reference numbers in the article "Professional misconduct or criminal negligence: when does the balance tilt?" by Veena Johari in the April-June 2014 issue of *IJME*. The corrected reference numbers may be read as follows:

Page 118, column 1, paragraph 1, line 5: reference no (2)

Page 118, column 1, paragraph 6, line 6: reference no (3)

Page 118, column 2, paragraph 2, line 15: reference no (4).