DISCUSSION

US-funded measurements of cervical cancer death rates in India: scientific and ethical concerns

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Abstract

Background: *Since 1998, randomised trials in India funded by the US National Cancer Institute (NCI) and the Bill and Melinda Gates Foundation have compared cervical cancer death rates among 224,929 women offered cervical screening to those among 138,624 women offered no screening whatsoever. To date, at least 254 women in unscreened control groups have died of cervical cancer. The United States Office for Human Research Protections (OHRP) determined that the subjects in the studies were not given adequate information for the purpose of providing informed consent. The determinations of the OHRP contradict assurances given by other American medical and bioethical leaders.*

Concerns: *Defective scientific design required inadequate informed consent. US-funded measurements of death rates may have needlessly delayed development of indispensable, life-saving public health infrastructure. US-funded measurements of incidence and death rates proved to be scientifically irreproducible and unreliable. Predictably, nothing was learned from these measurements that was not already known. Statistical bias embedded in measurement of death rates yielded the absurd conclusion that Papanicolaou screening does not prevent cervical cancer, leading to a marketing campaign for a proprietary human papillomavirus (HPV) screening test unaffordable for the women among whom death rates had been measured. Inexplicably, measurements of death rates among unscreened women were continued even after the mortality benefit of screening had been confirmed. Quality management of NCI-funded visual screening (VIA) in Mumbai failed catastrophically, with unsettling implications for VIA conducted by those with less expertise.*

Conclusions: *High-quality screening must be provided to all surviving unscreened women without further delay. US-based global health organisations should institutionalise a commitment to "improving health outcomes as rapidly as possible among as many people as possible." Those who suffered avoidable harm and death, as well as their families, should be promptly and fairly compensated. As another critic of these unfortunate studies concluded, "You can't let people die to show something you already know."*

Background

Since 1998, three separate randomised clinical trials of cervical screening have been conducted among Indian women of the lowest socioeconomic status in Mumbai (1,2), Osmanabad (3,4) and Tamil Nadu (5,6), with funding from the US National Cancer Institute (NCI) (1,2) and the Bill and Melinda Gates Foundation (BMGF) (3-6) through its Alliance for Cervical Cancer Prevention (ACCP). These studies have compared cervical cancer death rates among 224,929 women who were offered cervical screening with Papanicolaou smears, visual tests with acetic acid (VIA) or Qiagen Hybrid Capture 2® human papillomavirus (HPV) tests (HC2®) to those among 138,624 women who were offered no screening at all. To date, at least 254 women in unscreened control groups have died of cervical cancer (Table 1).

It is believed to be unethical to withhold effective health interventions from control groups unless the consequences are transient and trivial. What has been a cause of controversy is whether this standard should apply in poor areas of the world (7). Since 2004, concerns regarding US-funded measurements of cervical cancer death rates (8-17) and responses to some of these concerns (18-21) have been published in peer-reviewed journals. In 2009, a summary of these concerns was submitted to the BMGF Global Health Leadership Team (14), which did not respond. In 2011, the following cross-referenced four-point summary of concerns was submitted in writing (22) and in person (23) to the US Presidential Commission for the Study of Bioethical Issues (PCSBI), and subsequently, to the US Office for Human Research Protections (OHRP). It was then posted on a US Government website, according to instructions published in the US Federal Register (24).

1. Ongoing measurements of cervical cancer death rates appear to be scientifically gratuitous and, in addition, do not appear to satisfy ethical requirements of equipoise and informed consent.
2. Methodological bias has provided a false appearance of scientific meaning to these measurements of death rates.
3. A false appearance of scientific meaning has been used to publicise misleading claims about a proprietary cervical screening test (HC2®) that is unaffordable for the Indian population among whom it was studied.

4. Potential financial conflicts of interest exist between groups conducting the ongoing India studies and the manufacturer of the proprietary screening test about which misleading claims have been publicised.

The PCSBI did not respond to these concerns or refer them to other agencies. The OHRP has no authority to investigate BMGF-funded studies (3-6) because these studies received no funding from the US Department of Health and Human Services (HHS) (25). The OHRP referred concerns regarding misleading marketing claims to the US Food and Drug Administration (FDA). The OHRP determined that neither scientific pointlessness nor lack of equipoise violate HHS regulations pertaining to the protection of human subjects (25). In 2012, the OHRP determined that, in violation of HHS regulations, subjects in the NCI-funded study (1,2) had not been provided with adequate information on the differences between research procedures (eg no screening) and Papanicolaou screening, and that research subjects had not been informed in writing about seeking cervical screening outside the research context (26). The OHRP also determined that the institutional review board (IRB) of the study had failed to conduct continuing review at least once a year, or to maintain minutes of its meetings, or to meet quorum requirements (26).

The OHRP's determinations suggest that medical journals which published data obtained from research subjects whose consent had been improperly obtained have not complied with recommendations regarding the protection of research participants established by the International Committee of Medical Journal Editors (27). The OHRP's determinations appear to be inconsistent with the assurances of ACCP leaders, who had defended the US-funded measurements as having "been approved after undergoing extensive and required ethical review by US- or European-based institutions as well as by in-country academic and government ethical review boards"(18). The OHRP's determinations also appear to be inconsistent with assurances from the directors of the US Centers for Disease Control and Prevention (CDC) and US National Institutes of Health (NIH), who, prior to the PCSBI investigation ordered by President Obama (28), had concluded that unethical research funded by the US Government could not be carried out today (29). The OHRP's determinations appear to be inconsistent with the PCSBI's assurance to President Obama that current regulations "appear to protect people from avoidable harm or unethical treatment" (30).

NCI-funded investigators disputed the OHRP's determinations, claiming that "all women in the Mumbai trial (control and intervention arms) were counselled on Pap smear testing, given information on the centres nearby that offered the Pap smear and assured that they were free to get themselves screened if they so wished"(21). The NCI's Director of Global Health disputed the OHRP's determinations, claiming that "we looked at the ethics very carefully and felt them to be sound" (31). The President of the American Society of Clinical Oncology also disputed the OHRP's assertions, stating "there really was no wrongdoing there" (31). Since apparently no structures exist to resolve such ethical disputes, this article reviews the scientific as well as ethical concerns related to the US-funded measurements of cervical cancer death rates in India. The three cervical screening studies reviewed are entirely different from the BMGF-funded studies of HPV vaccination in India that were censured by the Parliament of India in 2013 (32).

Concerns

Defective scientific design required inadequate informed consent
Not every health intervention requires a clinical trial; sometimes, what is required is not a clinical trial, but the political will and resources to provide the care (7). Root cause analysis indicates that critical real-world obstacles to the effective prevention of cervical cancer involve people far more than technology (10). These obstacles can be attributed to lapses of political will and quality management, to which all preventive interventions are vulnerable (10). However, there is almost a knee-jerk tendency to respond to a lack of medical services with clinical trials (7). Partly, this is a matter of researchers responding by doing what they know how (and are paid) to do. However, researchers often subscribe to the view that only a clinical trial will convince policy-makers that something should be done (7).

Cervical screening is a secondary preventive intervention that reduces incidence rates and death rates of cervical cancer by detecting and treating high-risk "pre-cancerous" cervical lesions before these lesions progress to cancer. Since an increase in detection rates for these pre-cancerous lesions results in reductions of incidence rates and death rates of cervical cancer, it is generally accepted that increased detection rates constitute the best scientific proof of the value of any novel cervical screening approach (33). Measurements of incidence and death rates are consequently considered scientifically unnecessary in countries other than India. However, US-funded investigators claim that "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 pre-cancerous lesions and model-based studies of screening tests which are unlikely to drive public health policy changes on their own" (20).

Therefore, the essential scientific novelty of the controversial US-funded studies in India has been to collect outcomes measurements (ie incidence rates and death rates of cervical cancer) in addition to process measurements (eg disease-detection rates), presumably to drive policy change in India. Others have suggested that people should not be used to demonstrate exactly how much death results from lack of medical care; besides being ethically problematic, such demonstrations are not particularly convincing to policy-makers, who already know what is going on (7). World Bank policy-makers approved the routine implementation of VIA screening services in Tamil Nadu in 2004 (34), several years before any US-funded measurements of death rates were available. If, as appears likely, there are no policy-makers who required these measurements, then there was no reason to

collect such measurements in the first place.

The US Preventive Services Task Force (USPSTF) has determined that, among previously unscreened communities, Papanicolaou screening reduces cervical cancer rates by 60%–90% within three years of its introduction, and that these reductions in mortality and morbidity are "consistent and equally dramatic across populations" (35). Since a state of equipoise does not exist regarding the benefits of cervical screening (compared to no screening), the creation and maintenance of unscreened control groups in the US-funded studies in India required inadequate informed consent. If, at any time during the past 15 years, the 138,624 women in the unscreened control groups had been told the simple truth that cervical screening would lower their risk of death from cancer, they would have left the control groups and sought screening on their own, thereby nullifying a scientifically defective experimental design. It is thus difficult to presume that the BMGF-funded studies (3-6) are not compromised by the inadequate informed consent that, according to the OHRP's determinations, compromise the NCI-funded study.

It has been claimed that having unscreened control groups is ethically justified in India because no-screening is considered "standard care" (21). However, when India's Cancer Control Programme was converted into a national programme in 1985, one of its objectives was secondary prevention of cervical cancer (36). It is remarkable that the US-funded studies assumed that no-screening was "standard care" throughout India in 1998 and would remain so for the planned 18-year duration of these studies.

US-funded measurements may have needlessly delayed development of indispensable, life-saving public health infrastructure

In 1996, Indian investigators funded by India's Ministry of Health concluded that "the logistics of implementing visual cervical inspection in public-health service settings are considerable, and the input required may not be much inferior to that required for a cytology programme" (37). In 1999, the BMGF founded the ACCP on the extraordinary assumption that non-cytological approaches (rather than Papanicolaou screening) are the most likely preventive solutions for cervical cancer in developing countries (38). In 2004, Indian investigators funded by the BMGF claimed that "the financial and logistics burden of operating an organised screening programme based on cytology is considerable, and has encouraged the evaluation of alternative methods such as VIA" (5). The corresponding authors for the 1996 report funded by the Ministry of Health (37) and for the 2004 BMGF-funded report (5) were the same.

The ideological bias of the BMGF towards novel technologies as the best route for improving health outcomes in developing countries has been criticised as being potentially harmful (39). The Global Malaria Programme Director of the World Health Organisation warned that the Gates Foundation's determination to have its favoured research used to guide global health recommendations "could have implicitly dangerous consequences on the policy-making process in world health" (40). US-funded leaders remain "loath" to recommend the introduction of Papanicolaou screening to high-risk communities with no cervical screening programmes currently in place (14,41), and boast of "driving nails into the coffin" of Papanicolaou cytology (42).

Papanicolaou screening is feasible anywhere that cervical screening is appropriate (8). Papanicolaou cytology will remain an essential technological component of future cervical cancer prevention programmes (10). It is paradoxical to cite shortages of indispensable, life-saving infrastructure (such as cytotechnologists) as reasons not to develop more (8). De novo establishment of Papanicolaou screening in southern Viet Nam during the 1990s (43) led to a 50% reduction in the incidence rate of cervical cancer within five years (14). NCI experts have acknowledged the success of Papanicolaou screening in Viet Nam (44). The strategy used to achieve the effective prevention of cervical cancer in Viet Nam was to stimulate consumer demand for Papanicolaou screening services while lowering the prices for these services (14). One wonders where women in India might be today if US-funded leaders had accepted the conclusions of the 1996 study (37) and stimulated rather than suppressed consumer demand for Papanicolaou screening services while conducting research on HPV-based and VIA-based approaches.

US-funded measurements proved to be scientifically irreproducible and unreliable

The rationale for initiating a 10-year study of "once in a lifetime" VIA screening in Tamil Nadu in 2000 (5,6) after initiating an 18-year study of "four in a lifetime" VIA screenings in Mumbai in 1998 is unclear (1,2). It is also unclear why a 10-year study of "once in a lifetime" VIA screening was initiated in Tamil Nadu in 2000 (5,6) after a 10-year study of "once in a lifetime" VIA, Papanicolaou, and HC2® screening had been initiated in Osmanabad in 1999 (3,4).

Nevertheless, the puzzling redundancy of US-funded studies demonstrated that their measurements of incidence rates and death rates were scientifically irreproducible and unreliable. VIA reduced both the incidence and death rates of cervical cancer in Tamil Nadu (Table 2). In contrast, neither Papanicolaou smears, nor HC2®, nor VIA reduced the incidence rates in Osmanabad (Table 2). Neither Papanicolaou smears nor VIA reduced the death rates in Osmanabad (Table 2). VIA reduced the death rates, but not the incidence rates, in Mumbai (Table 2). HC2® reduced the death rates, but not the incidence rates, in Osmanabad (Table 2). It is puzzling how cervical screening can reduce death rates without reducing incidence rates, further underscoring the scientific unreliability of US-funded outcomes measurements.

Predictably, nothing was learned from these death rate measurements that was not already known

Even if one assumes that measurements of death rates are necessary to drive policy change in India, the inclusion

of unscreened control groups in such measurements is scientifically pointless. Cervical screening and cessation of smoking both received "A" recommendations from the USPSTF in the absence of randomised trials confirming their effectiveness. Randomised trials that compare cervical screening to no-screening to confirm that cervical screening prevents cervical cancer are as scientifically pointless as randomised trials that compare smoking to no-smoking to confirm that no-smoking prevents lung cancer (8). A long-standing concern has been that experimental measurements of the death rate of cervical cancer among women not offered cervical screening would not change clinical practice (8). If cervical screening (compared to no-screening) correlated with reductions in death rates, the result would be scientifically pointless; if cervical screening (compared to no-screening) failed to correlate with such reductions, the result would be considered absurd and not generalised to other settings (8). The Osmanabad study is the first in history to conclude that Papanicolaou screening, performed correctly, does not reduce either the incidence rates or death rates of cervical cancer (4). Predictably, this absurd conclusion has not caused clinicians to abandon Papanicolaou screening. Just as predictably, because a state of equipoise does not exist regarding the benefits of cervical screening, nothing was learned from the US-funded measurements of death rates that was not already known.

Statistical bias embedded in measurement of death rates yielded the absurd conclusion that Papanicolaou screening does not prevent cervical cancer, leading to a marketing campaign for a proprietary HPV screening test unaffordable for the women among whom death rates had been measured

The absurd apparent failure of Papanicolaou screening to prevent cervical cancer in Osmanabad was attributable to peculiar statistical bias, skewed in favour of HC2® screening, embedded in the measurement of death rates (12). Based on scientifically reliable process measurements, Papanicolaou smears decisively outperformed HC2® in Osmanabad by demonstrating equal disease-detection rates and lower test-positivity rates (Table 2). False and misleading claims that the performance of the HC2® test was superior were published in the *New England Journal of Medicine* (4), and were applauded in the *New York Times* (42) and praised by NCI experts (45). No mention whatsoever was made of the profound ethical concerns involved. These claims seemed to vindicate the ACCP's extraordinary founding assumption that non-cytological approaches (rather than Papanicolaou screening) are the most likely preventive solutions for cervical cancer in developing countries. These false and misleading claims launched a carefully orchestrated global marketing campaign for a proprietary HPV test that was unaffordable for those among whom death rates had been measured. The introduction of "open-source" HPV tests may prove problematic, as the International Agency for Research on Cancer warns that "increased competition resulting in diminishing market share and reductions in the cost of testing might lead HPV test manufacturers to relax their standards of quality. Such a scenario could prove disastrous in many respects, since there are theoretically many more variables that can affect the performance of HPV testing than there are for cytology-based screening" (46).

At the same moment the death rates from Osmanabad were published, Qiagen Corporation (which manufactures and markets HC2®) issued a press release titled "Landmark study in *New England Journal of Medicine* shows HPV testing significantly reduces deaths from cervical cancer, compared to other methods including Pap" (12). In 2013, the US FDA determined that it had insufficient information to pursue compliance actions against Qiagen, since the claim that "HC2® significantly reduces deaths from cervical cancer compared to other methods" was, by that time, no longer found in Qiagen's labelling, website or advertisements, and since the FDA cannot regulate claims published in a scientific journal (47). The ACCP's coordinating agency (PATH; Seattle, Washington, USA) has ignored requests to fully disclose the terms of its financial partnership with Qiagen, including any arrangements for revenue-sharing from future sales of HPV tests (48).

US-funded investigators reportedly started offering HC2® screening to women in the previously unscreened control group in the Osmanabad trial in January 2011 (49). However, if US-funded investigators consider measurements of death rates to be scientifically reliable, then HC2® screening should be offered to women in the Papanicolaou and VIA screening groups as well, as HC2® screening and HC2® screening alone was associated with reductions in the death rates in Osmanabad. The delay in offering screening to the unscreened until January 2011 is unsettling because significant reductions in death rates had been documented in the Osmanabad HC2® study group by April 2009 (4).

Inexplicably, measurements of death rates among unscreened women were continued even after the mortality benefit of screening had been confirmed

By 2007, a single round of VIA screening in Tamil Nadu had reduced the incidence rates of cervical cancer by 25% and the death rates by 35% (Table 2). That result was scientifically pointless: by 1992, Indian investigators had determined that a single round of cervical screening would reduce the incidence of cervical cancer in India by 25% (50,51). Remarkably, US-funded investigators "plan to continue the follow-up of study population for cervical cancer incidence and mortality for several years to have information on long-term effect of the single intervention and to infer on screening intervals based on the extent of shrinkage of mortality reduction following single intervention" (6). To date, it is uncertain whether any screening has been offered to women in the unscreened control groups in Tamil Nadu. It is unsettling that measurements of death rates among these women were continued even after the mortality benefit of VIA had been established there. It is also unsettling that such measurements were continued among unscreened women in Mumbai and Osmanabad even after the mortality benefit of a single round of VIA screening had

been established in Tamil Nadu. Even if one were to assume that measurements of death rates and the existence of no-screening arms were justified in the first place, the no-screening arms in all three US-funded studies should have been closed after the demonstration of the mortality benefit of VIA had been documented in 2007. In 2013, the NCI's Director of Global Health praised the NCI-funded results as "amazing," "remarkable," and "very exciting," (31) and NCI-funded investigators claimed that, prior to the study in Mumbai, there had been no randomised evidence that VIA leads to a reduction in mortality from cervical cancer (21). This praise and these claims inexplicably ignore the predictions published in the early 1990s (50,51), as well as randomised evidence from Tamil Nadu published in 2007 (6).

Quality management of NCI-funded VIA in Mumbai failed catastrophically, with unsettling implications for VIA conducted by those with less expertise

After three rounds of VIA screening in Mumbai, the number of deaths from cervical cancer was greater in the VIA screening arm than in the unscreened control group (Table 2). The failure of three rounds of VIA screening to lower either incidence or death rates in Mumbai, when a single round had reduced both incidence and mortality in Tamil Nadu, can be attributed to the extraordinarily poor quality of VIA in Mumbai, as reflected in the extraordinarily low rates of disease-detection using VIA documented there (Table 2).

US-funded investigators acknowledge that "because visual tests, like cytology, are essentially subjective, quality control is an important issue…close monitoring of test-positivity and disease-detection rates are essential to maintain good standards of visual testing" (52). These essential guidelines were inexplicably ignored in Mumbai. Disease-detection rates using VIA in the NCI-funded study in Mumbai were 40 times lower than those in another BMGF-funded study in Mumbai (a cross-sectional study of the three screening methods) (53)[1], and 10 times lower than the disease-detection rates for no-screening in Tamil Nadu and Osmanabad (Table 2). The NCI-funded investigators' claims that in Mumbai VIA "detected a very large number of pre-invasive cancers" (21) are contradicted by their own measurements of disease-detection rates (Table 2). Remarkably, during the second round of screening in Mumbai, the disease-detection rate using VIA was lower than that for no-screening (Table 2). It is, therefore, uncertain whether any screening whatsoever took place in Mumbai. It appears that for 15 years, neither US-funded investigators nor the NCI Data Safety Monitoring Board noted the catastrophic failure of quality management of VIA in Mumbai. This has disturbing implications for real-world quality management of VIA in settings with lower levels of expertise. Close monitoring of VIA test-positivity and disease-detection rates will be essential in all settings, including the World Bank-supported VIA screening programme in Tamil Nadu (34). However, it is not possible to verify the existence of VIA screening activities, or to monitor disease-detection rates by VIA, when VIA is used without confirmatory tissue biopsies (10).

Following the OHRP's assertion, the IRB of the study decided unanimously to offer VIA screening to all surviving subjects in the NCI-funded study's unscreened control group in Mumbai (54). However, due to the extraordinarily poor quality of VIA screening in Mumbai, a single round of screening is unlikely to benefit these subjects.

Conclusions

The poor suffer disproportionately not only because of the world's indifference to their poverty, but also because of ineffective efforts by those who do care (55). Research and commercial interests produced significant obstacles to the achievement of effective cervical cancer prevention in Viet Nam (56). It appears that influential global health organisations are currently promoting research and commercial interests at the expense of appropriate public health goals. Opportunity costs, borne most acutely by those least privileged, are associated with prioritising research on novel interventions in settings where established interventions are feasible but unavailable (8). One of the most important lessons learned from effective cervical cancer prevention in Viet Nam is that cervical cancer prevention efforts are more effective when leaders are ideologically committed to the appropriate public health goal of "improving health outcomes as rapidly as possible among as many people as possible" and assimilate the policy implications of that commitment (14). Competing ideological commitments engender imprudent yet commercially useful alternative policies prone to decelerate global reductions in mortality (14), as exemplified by the US-funded measurements of cervical cancer death rates in India.

High-quality cervical screening (defined by locality-specific process measurements) must be offered without further delay to the surviving women in all unscreened control groups of the US-funded studies. NIH, NCI, CDC and BMGF leaders should explicitly incorporate the commitment "to improve health outcomes as rapidly as possible among as many people as possible" into the mission statements of their respective global health institutions. The policy implications of that commitment, as explained in detail elsewhere (14), include indispensable roles for Papanicolaou cytotechnology (even in HPV-based and VIA-based screening programmes) and greatly diminished roles for HPV vaccination in resource-constrained settings. Those and the families of those who suffered avoidable harm and death should be promptly and fairly compensated. As another critic of these unfortunate studies concluded, "You can't let people die to show something you already know" (57).

Disclosure

I have no relevant financial conflicts of interest. I am certified by the American Board of Pathology in Anatomic Pathology and Clinical Pathology. I am not certified in Cytopathology or any other subspecialty.

Table 1
Summary of results from US-funded studies of cervical screening in India

Study location/ funding source	Year started	Screening test used	#Eligible women	#Positive screening tests	#Screen-positive women with CIN2+ on biopsy	#Screen-negative or unscreened women[a] with CIN2+ on biopsy	#Cervical cancer deaths
Mumbai (1) Round1/NCI*	1998	VIA	75,360	672	38	n/a	n/a
Mumbai (1) Round 1/NCI	1998	None	76,178	n/a	n/a	8[a]	n/a
Mumbai (1) Round 2/NCI	2000	VIA	71,500	791	20	n/a	n/a
Mumbai (1) Round 2/NCI	2000	None	72,145	n/a	n/a	28[a]	n/a
Mumbai (1) Round 3/NCI	2002	VIA	67,530	642	35	n/a	18 (after 3 rounds)
Mumbai (1) Round 3/NCI	2002	None	67,664	n/a	n/a	14[a]	15 (after 3 rounds)
Mumbai (2) Round 4/NCI	2004	VIA	n/a	n/a	n/a	n/a	67 (after 4 rounds)
Mumbai (2) Round 4/NCI	2004	None	n/a	n/a	n/a	n/a	98 (after 4 rounds)
Mumbai (53)/ BMGF	2001	VIA	4,039	385	54	31	n/a
Mumbai (53)/ BMGF	2001	Pap smears	4,039	43	50	31	n/a
Mumbai (53)/ BMGF	2001	HC2®	4,039	217	45	25	n/a
Osmanabad (4)/ BMGF	1999	VIA	34,074	3,733	277	100[b]	56
Osmanabad (4)/ BMGF	1999	HC2®	34,126	2,812	318	62[c]	34
Osmanabad (4)/ BMGF	1999	Pap smears	32,058	1,787	345	91[d]	54
Osmanabad (4)/ BMGF	1999	None	31,488	n/a	56[e]	118[a]	64
Tamil Nadu (6)/ BMGF	2000	VIA	49,311	3,088	285	100[f]	83
Tamil Nadu (6)/ BMGF	2000	None	30,958	n/a	n/a	158[a]	92

[a] CIN2+ cases are detected among no-screening control groups when symptomatic women with invasive cervical cancer seek clinical consultation.

[b] 34 cases of subsequent incident cancer (ie diagnosed more than 3 months after a positive screening test), 25 cases among women with negative VIA tests, 41 cases among women eligible for screening yet not screened

[c] 22 cases of subsequent incident cancer (ie diagnosed more than 3 months after a positive screening test), 8 cases among women with negative HC2® tests, 32 cases among women eligible for screening yet not screened

[d] 27 cases of subsequent incident cancer (ie diagnosed more than 3 months after a positive screening test), 22 cases among women with negative Papanicolaou smears, 42 cases among women eligible for screening yet not screened

[e] 56 cases came from 1946 women assigned to control group who opted out for Papanicolaou screening

[f] 29 screen-negative women, 61 women assigned to screening but unscreened, and 10 women screen-positive for CIN and later diagnosed with cancer

* All numbers in parenthesis in Column 1 are citation numbers to the studies.

Abbreviations:

CIN2+: includes pre-cancerous lesions (cervical intraepithelial neoplasia grade 2, cervical intraepithelial neoplasia grade 3, and adenocarcinoma in situ), as well as invasive cervical carcinoma

NCI: US National Cancer Institute

BMGF: Bill and Melinda Gates Foundation

Pap smears: Papanicolaou cytology smears

VIA: visual screening with acetic acid

HC2®: Qiagen Hybrid Capture 2® human papillomavirus test

n/a: not available

Table 2

Process measurements and outcome measurements from US-funded studies in India

Study location/ funding source	Screening test used	Process measurements		Outcomes measurements		Reported effect of screening on cervical cancer incidence rates[d]	Reported effect of screening on cervical cancer death rates[d]
		Test-positivity rates[a] (%)	Disease-detection rates[b] (%)	Cervical cancer incidence rates[c]	Cervical cancer death rates[c]		
Mumbai (1) Round 1/NCI*	VIA	0.89	0.05	n/a	n/a	NSS	NSS
Mumbai (1) Round 1/NCI	None	n/a	0.01[e]	n/a	n/a	n/a	n/a
Mumbai (1) Round 2/NCI	VIA	1.1	0.03	n/a	n/a	NSS	NSS
Mumbai (1) Round 2/NCI	None	n/a	0.04[e]	n/a	n/a	n/a	n/a
Mumbai (1) Round 3/NCI	VIA	0.95	0.05	n/a	n/a	NSS	NSS
Mumbai (1) Round 3/NCI	None	n/a	0.02[e]	n/a	n/a	n/a	n/a
Mumbai (2) Round 4/NCI	VIA	n/a	n/a	26.7	n/a	NSS	31% reduction
Mumbai (2) Round 4/NCI	None	n/a	n/a	27.5	n/a	n/a	n/a
Mumbai (53)/ BMGF	VIA	9.5	1.3	n/a	n/a	n/a	n/a
Mumbai (53)/ BMGF	Pap smears	1.1	1.2	n/a	n/a	n/a	n/a
Mumbai (53)/ BMGF	HC2®	5.4	1.1	n/a	n/a	n/a	n/a
Osmanabad (4)/ BMGF	VIA	11	0.8	58.7	20.9	NSS	NSS
Osmanabad (4)/ BMGF	HC2®	8.2	0.9	47.4	12.7	NSS	50% reduction
Osmanabad (4)/ BMGF	Pap smears	5.6	1.1	60.7	21.5	NSS	NSS
Osmanabad (4)/ BMGF	None	n/a	0.6[e]	47.6	25.8	n/a	n/a
Tamil Nadu (6)/ BMGF	VIA	6.3	0.6	75.2	39.6	25% reduction	35% reduction
Tamil Nadu (6)/ BMGF	None	n/a	0.5[e]	99.1	56.7	n/a	n/a

[a] Test-positivity rate = #positive screening tests (from Table 1)/#eligible women (from Table 1)

[b] Disease-detection rate = #women with CIN2+ on biopsy (from Table 1)/#eligible women (from Table 1). Numbers of eligible women were used as denominators so that disease-detection rates from screening tests could be compared to disease-detection rates from no-screening.

[c] Age-standardised rate per 100,000 person-years

[d] Compared to no-screening

[e] CIN2+ cases are detected in no-screening control groups when symptomatic women with invasive cervical cancer seek clinical consultation.

* All numbers in parenthesis in Column 1 are citation numbers to the studies.

Abbreviations

CIN2+: includes pre-cancerous lesions (cervical intraepithelial neoplasia grade 2, cervical intraepithelial neoplasia grade 3 and adenocarcinoma in situ), as well as invasive cervical carcinoma
NCI: US National Cancer Institute
BMGF: Bill and Melinda Gates Foundation
Pap smears: Papanicolaou cytology smears
VIA: visual screening with acetic acid
HC2®: Qiagen Hybrid Capture 2® human papillomavirus test
n/a: not available (or not applicable)
NSS: not statistically significant

Note

[1] *Corrections have been made in the placing of references with the previously numbered Reference no.2 now no. 53 and details of the BMGF-funded Mumbai study have been given.*

References

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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