**HPV Vaccine Splits Cochrane Board Wide Open**

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Cervical cancer, with 500,000 new cases each year, accompanied by 250,000 annual deaths, is not a disease to be trifled with. It happens to be the second most common cancer in women (1). Almost all cases of cancer of the cervix are due to infection with the human papillomavirus (HPV). The biggest culprits are HPV type 16 and 18. Two vaccines are available on sale against the HPV 16 and HPV 18, one of them is also effective against HPV 6 and HPV 11 , responsible for genital warts. The vaccine is administered as 3 intramuscular injections over 6 months(2-4). The human papillomavirus is sexually transmitted, which means females who have attained puberty are particularly susceptible. Persistence infection with HPV results in alterations of cervical epithelial cells after a period of 5 years. Around 10% of infected women go on to develop histological changes graded as cervical intraepithelial neoplasia (CIN 1), CIN 2 and CIN 3. The next grade is termed carcinoma in situ or CIS. The chances of developing full blown cervical are increased considerably once the cellular changes develop, but are still are as low as 1% to 10%, which means that a substantial number of females with precancerous cellular changes resolve spontaneously. Invasive cervical cancer arises over many years , peaking between 35 and 55 years of age (5). The HPV vaccine has no role once a person has become infected. Substantial reduction in HPV infection have been recorded, but effect on cervical cancer remains to be established due to the long lag time in development of invasive cancer subsequent to HPV infection. A systemic review of HPV vaccination of at least 50% in high income countries reported that HPV 16 and 18 infections significantly deceased by 68%, while anogenital warts decreased significantly by 61% in girls 13 to 19 years. Another recent meta analysis of observational studies on quadrivalent HPV vaccination has reported maximal reductions of approximately 90% for HPV 6/11/16/18 infection, approximately 90% for genital warts, approximately 45% for low grade cytological cervical abnormalities, over a 10 year period (6-8)

Cervical cancer is the second common cause of cancer mortality in women in India, with more than 122,000 new patients each year accompanied by almost 70,000 deaths.In fact 85% of cervical cancer cases are in low and middle income countries. Twenty five percent of cervical cancer deaths in the world occur in India. Despite the dire statistics the Ministry of Health and Family Welfare continues to mull over the decision to include the HPV vaccine in the national immunisation program. The reluctance of the government is largely because of a 2012 writ petition (public interest) filed against the vaccine in the Supreme Court, and political pressure by one of its own affiliates. With a single dose costing almost $ 50 in India, any Indian government would blanch at the idea of putting in billions of dollars on a single vaccine. The HPV vaccine is however available commercially in the private sector.

An excellent randomised study from India (9) reported that a single round of screening for HPV involving more than 130,000 women substantially reduced the incidence of advanced cervical cancer and cervical related mortality within 8 years. Screening therefore would be essential in women aged 25-40 years to manage pre cancerous cervical lesions and also cancer itself. A much earlier and probably the best intervention would be preventing infection by HPF; this is where a vaccine comes into play. We already have data demonstrating significant reduction in HPV infection by the vaccine.

The public interest litigation writ filed in the Supreme Court provides graphic details of the only very badly managed HPV vaccine trial conducted by an American NGO and the Indian Council of Medical Research. The trial created an uproar when it was realised that informed consent printed in English were signed by school principals and hostel wardens on behalf of girls aged as little as 10 years. Almost 25,000 young tribal and rural girls were vaccinated technically without their or their parents consent. Moreover 7 girls died, but an investigation conducted by the federal government could not confirm association or causality with the vaccine. The writ petition states that half of the girls vaccinated were either anaemic or malnourished. Also that syringe needs were not always sterilised and girls under 10 years were vaccinated. The final verdict is waited ; in terms of speed the Supreme Court is no Usain Bolt. The national technical board on vaccination ,however ,has recommended that HPV vaccine be included in the federal immunisation program (10-11)

A report from National Health England in 2017 suggested that HPV infection had dropped by 86% subsequent to HPV vaccination of girls aged 16-21 from 2006 to 2010 (12). The Australian story is even better; 79% of 15 year old girls and 73% of 15 year old boys were vaccinated in 2016. Rate of HPV in women aged 18 to 24 dropped from 22.7% to 1.1% (13).

We can now against the above background wade into the unprecedented controversy enveloping the Cochrane Collaboration. The Cochrane group has been for more than 2 decades arguably providing the highest quality systemic reviews on various issues. The quality, rigour, and integrity of Cochrane reviews have been considered outstanding by most if not all academics. Moreover Cochran is globally recognised as probably the last bastion standing against commercial interference and manipulation of clinical trials by Big Pharma. It therefore came as a huge surprise to most in the academic world that a senior investigator of sterling scientific reputation has been unceremoniously expelled from Cochrane because of unbecoming behaviour.

Apparently the trigger was a scathing critique published in the British Medical Journal Evidence Based Medicine in July 2018 (14) of a systemic review by Cochrane on the safety and efficacy of the HPV vaccine in May 2018 (12). The critique was authored by 3 senior investigators of the Cochrane group itself, with the second author being the much lauded Peter Gotzsche. I repeat this damaging critique of the the systemic review on HPV vaccine by Cochrane ,was authored by investigators from within the Coichrane group itself. Public criticism of a systemic review published by Cochrane by its own senior researchers without prior information to the Cochrane management did not go down well with the CEO of Cochrane, who ensured that Peter Gøtzsche got the boot for alleged persistent “ bad behaviour” that brought “disrepute” to the organisation. The expulsion was backed by the findings of an independent enquiry begun months earlier by a senior London lawyer . Four board members promptly resigned in protest from the Cochrane board , in support of Gøtzsche . The voting had been 6 against 5 in favour of expulsion, with one abstaining. Gøtzsche could not vote.

The expulsion of Gotzsche not only exercised a lot of academic minds, but also sparked numerous blogs and comments in many prestigious medical journals. Allegations and counter allegations continue to be hurled since that black 13 September day expulsion.. It would be pretentious and fool hardy to comment on this controversy from thousands of miles away in Delhi. Especially as one does not personally know any of the players in this scientific storm.But one could examine data published on this controversy, with particular attention to the chronology of events provided by the players themselves against the background of the high prevalence of cervical cancer and also the fact that science of any kind surely looms larger than an individual or a group of scientists. For instance albeit on a lighter note, baseball sell always be bigger than Babe Ruth or Lou Gehrig, and in the same breath cricket will always remain a bit larger than ‘The Don ‘or Tendulkar. Elida Kipchoge has smashed the marathon record by 78 seconds last week for a new record of 2:01:39, a staggering achievement whichever way you look at it, but this record too shall be broken in times to come. Newton said it best, his accomplishments were achieved by climbing on the shoulders of his predecessors. Science does not necessarily always progress in a linear manner, it develops erratically and haphazardly by millimetres, and at times even retrogradely. Mistakes have been made unknowingly and even wilfully, but we have traveled a considerable distance since John Snow figured out that cholera in the London of 1854 was caused by contaminated water. No single physicist, chemist, or botanist can claim to be the final or the only word.

Tom Jefferson the third author of the critique has posted a blog (16) in which he concedes right at the outset that his views on “ Brother Peter” may not be “impartial “ blog by one of the 3 authors of the critique. Jefferson in his defence of Gøtzsche, recognises Gotzsche as a man of “notable accomplishments” despite a “brash style”. Maybe , Jefferson tries to make the case that Gøtzsche has a heart of gold within an hard exterior. The “notable accomplishments” being a realistic reassessment of the use of mammography and opening up of the European Medical Agency regulatory submissions. Jefferson, however, goes on to reveal that a “ personality clash” had been simmering between Peter and the CEO for quite some time. This feud or ego clash, I believe, must have hit critical mass when the critique of the HPV vaccine appeared in the BMJ EBM. The timing of the critique may be important. A lot of bad blood going around for the previous quite a few months has initiated an independent inquiry of alleged repeated “bad behaviour” by Gotzsche. That appears to be the prerogative of the CEO to put Gotzsche under pressure. Gotzche seizes his opportunity when the vaccine review gets published in May, to counterattack by July with his stinging critique, having by his side Jefferson and Lars Jorgensen (the first author). Could the CEO have now been infuriated enough to ensure that Gotzsche was expelled as soon as possible? His anger must surely have been amplified by the fact that the authors of the critique went public despite being members of senior Cochrane investigators. He most probably was notified or forewarned of the impending public criticism. We now have some idea of the chain one events. A simmering ego clash, an independent enquiry into complaints against Gotzsche, publication of a systemic review of the HPV vaccine, which is then pounced upon by Gotzsche and Jefferson in a no holds barred manner to tear it own to shreds. The critique could be considered a form of activism if no prior information was given to the Cochrane organisation. Gotzsche heads the Nordic Cochrane Centre was published without informing Cochrane . Anyway the war escalated to a point of no return because the CEO played his hand. Jefferson now wants the Cochrane Body be reconstituted, with members involved in the controversy not being permitted to stand for re-election. Sage advice from a person who directly or indirectly triggered an unnecessary controversy in a globally respected organisation.

Now coming to the critique itself. Cochrane had published its systemic review on the HPV vaccine in May 2018, with the conclusion that the vaccine is effective against cervical precancer, without significant increase in adverse effects. By July 2018 the the BMJ EBM came out with the searing critique that made serious charges against the Cochrane review, ranging from “missing nearly half of the eligible trials” to ignoring conflict of interest. The first charge was that bias was manifest “with nearly half of the trials and half of the participants missing” in the Cochrane review. The 3 critique authors had prepared an index (in January 2018) of more than 200 HPV vaccine trials and claimed to have provided the document to the review authors. These trials were collected from clinical trial registers and clinical case studies rather than publication in journals alone. The Cochrane review had included 26 randomised trials; the critique authors presented another 20 trials that had been completed. Cochrane was compelled to review its own review by a group of fresh independent investigators who found that the HPV review had missed out on only 5 trials, and that on their addition there was no discernible difference in the conclusions of the original review. Cochrane has also given the assurance that the review will be updated in the near future as is customary.

The second serious charge made in the critique is that the Cochrane review deliberately concealed adverse events. They elaborate on the fact that postural orthostatic tachycardia syndrome (POTS) has been observed with the HPV vaccine. They also write that the vaccine manufacturer Sanofi did not look for symptoms of “dizziness, palpitations, rapid heart rate, tremor, fatigue and fainting” but instead noted symptoms of “postural dizziness, orthostatic intolerance, and palpitations and dizziness.” I as a clinician ( an interventional cardiologist) find this charge a bit fanciful if not extreme. A vaso vagal attack, postural hypotension, neurogenic syncope, or sinus node disease - may all present with postural dizziness or palpitations and dizziness, as also with dizziness, palpitations and a rapid heart rate. Moreover POTS is a fairly new disease entity with a lot of gaps in its prevalence, ethology, pathogenesis, and treatment. Cardiologists are well aware of neurogenic syncope, which may or may not be treated with a pacemaker depending on the extent the heart rate drops. Also almost all patients getting a permanent pacemaker for a conduction defect in the heart complain of some form of giddiness or black out. Symptoms in POTS are more or less similar. One requirement is that light headedness or giddiness accompanied by palpitations comes about on standing from a lying position in a young woman. It has been suggested that POTS is an autoimmune problem but this is still to be confirmed (17-19) The given hypothesis is that auto-antibodies are directed against cholinergic ganglion, but the treatment ( volume over load plus salt or beta blocker ) is symptomatic so far. Crucially POTS will be difficult to distinguish from the light headedness complained by patients of depression or anxiety.The point I am making is that I wonder how the critique authors came to the conclusion that the causative culprit is the HPV vaccine, especially when prevalence of POTS itself is largely unknown. How does a clinician differentiate a simple faint in a teen age girl ( a vast vagal ) from POTS ? Some Japanese researchers have suggested that POTS is caused post HPV vaccination because of prolonged high antibody titres and contamination of the vaccine by virus and bacterial particles (20) These concerns are yet to be validated but HPV vaccination has dropped drastically in Japan.

The critique points out that all but one trial was funded by the industry and provide the “Costa Rica trial” as an example. The Costa Rica trial, however was funded by the government ( hence tax payer money) albeit the vaccines were provided by the manufacturer. Another issue posed by the critique is that most of the comparators used in the control group were strictly speaking not placebos but instead aluminium containing adjuvants, which are recognised to produce side effects. I do not have the technical knowledge to be sure whether the HPV vaccine can be produced minus an adjuvant, but I doubt if a young woman will mind prevention of invasive cervical cancer at the cost of pain, swelling or redness at the injection site.

The critique elaborates that there were more deaths in the HPV vaccine cohorts. The total number of deaths were 51 in the vaccine group versus 39 in the comparator groups. The critique authors appear mystified that these deaths are termed “chance occurrence” by the review authors. Also that the review did not provide actual number of deaths. This surely is an ineffective arrow because the review made it clear that the rates of death were similar overall (11/10,000 in controls versus 14/10000 in vaccinated). The critique insist that increased deaths are due to the HPV vaccine without presenting evidence. We are presented with a speculation countering a speculation form the other side. A difference of 12 deaths in more than 70,000 subjects may not be clinical meaningful even if the P value dips beneath the magic 0.05. Crucially, there is no evidence provided as to the cause of these deaths. Also more than 250 million doses of the HPV vaccine have been administered globally.

The troika (3 authors of the critique) also have a quarrel with the surrogate endpoints employed by the Cochrane review. They rightly point out that most women with a CIN 2 lesion may not progress to invasive cervical cancer. But their conclusion that this pre cancerous lesion should not be used as an end point is misplaced, because even if we presume that a CIN 2 will not evolve to invasive cancer the reverse cannot be expected, that a non CIN 2 lesion will develop into invasive cancer. Hence reduction in rates of CIN 2 or CIN 3 by the HPV vaccine, should be taken as a positive sign of efficacy. Moreover a pre cancerous lesion of the cervix cannot be ethically ignored.

Undoubtedly Gotzsche has been champion detector of methodology flaws in clinical trials, as also unhealthy influences of the industry on them. That the industry is constantly trying to spin data is well known, that editors of top medical journals have compromised on the quality of scientific rigour in their publications, and that conflict of interests despite extensive attempts still thrive in academia, is well documented. But one has to strike the right balance, the baby should not be thrown out with the bath water. One should not in the din and glare of the current crisis ignore the fact that millions of lives are at stake. Criticism for the sake of criticism behind a desire for applause cannot be justified. A clinician’s paramount responsibility is to treat the sick, armed with evidence that has been reasonably vetted. It is therefore imperative that Cochrane sorts out its house at the earliest to retain its scientific sheen. One hopes that Cochrane updates the HPV vaccine review soon keeping in mind some of the issues raised by the critique; ensuring that no new author has industrial ties. It may also be a reasonable idea if a couple of clinicians are incorporated in all systemic reviews to achieve greater depth and credibility.

The current imbroglio, rather unnecessary, needs to be rectified at the earliest , by placating bruised egos, and reinstalling a complete board minus temperamental researchers to re-inspire the requisite confidence in the Cochrane Collaboration. Personality clashes cannot be permitted to bring down the most respected international research organisation on the planet. A vaccine should not be permitted to split open Cochrane, A vaccine should not be permitted to split Cochrane wide open.

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