IN THE HIGH COURT OF DELHI, AT NEW DELHI

(CIVIL ORIGINAL JURISDICTION)

Writ Petition (Civil) No. ..... of 2015

A WRIT PETITION IN PUBLIC INTEREST UNDER ARTICLE 226 OF THE CONSTITUTION OF INDIA SEEKING A WRIT DIRECTING THE RESPONDENTS TO PROVIDE COMPLETE DATA OF THE RESULTS OF A MULTICENTRE CLINICAL TRIAL OF ROTAVIRUS VACCINE DONE ON INFANTS.

MEMO OF PARTIES

In the matter of Public Interest Litigation:

JACOB PULIYEL, MD, MRCP MPhil

ST STEPHENS HOSPITAL

DELHI 110054 ..... THE PETITIONER

VERSUS

THE UNION OF INDIA

THROUGH ITS SECRETARY

MINISTRY OF HEALTH & FAMILY WELFARE

NIRMAN BHAWAN, NEW DELHI-110001 …RESPONDENT NO. 1

THE UNION OF INDIA

THROUGH ITS SECRETARY

DEPARTMENT OF BIO-TECHNOLOGY

MINISTRY OF SCIENCE AND TECHNOLOGY

6TH-8TH FLOOR, BLOCK 2

CGO COMPLEX, LODHI ROAD

NEW DELHI - 110 003 …RESPONDENT NO. 2

CHRISTIAN MEDICAL COLLEGE

THROUGH ITS DIRECTOR

CMC VELLORE, 632004

TAMIL NADU …RESPONDENT NO. 3

NATIONAL TECHNICAL ADVISORY

GROUP OF IMMUNIZATION (NTAGI)

THROUGH ITS CHAIRPERSON

MINISTRY OF HEALTH & FAMILY WELFARE

NIRMAN BHAWAN, NEW DELHI-110001 …RESPONDENT NO. 4

PRASHANT BHUSHAN / NEHA RATHI
(ADVOCATES FOR THE PETITIONER)
ENROLMENT NO. D/200/83
301, NEW LAWYERS CHAMBERS
SUPREME COURT OF INDIA
NEW DELHI-110001

NEW DELHI
DATED: ___ JULY 2015

IN THE HIGH COURT OF DELHI, AT NEW DELHI

(CIVIL ORIGINAL JURISDICTION)

Writ Petition (Civil) No. ..... of 2015

IN THE MATTER OF PUBLIC INTEREST LITIGATION:

Jacob Puliyel …… Petitioner

Versus

Union of India & Ors. …… Respondents

A WRIT PETITION IN PUBLIC INTEREST UNDER ARTICLE 226 OF THE CONSTITUTION OF INDIA SEEKING A WRIT DIRECTING THE RESPONDENTS TO PROVIDE COMPLETE DATA OF THE RESULTS OF A MULTICENTRE CLINICAL TRIAL OF ROTAVIRUS VACCINE DONE ON INFANTS

To,

THE HON'BLE CHIEF JUSTICE OF DELHI AND HER COMPANION JUDGES OF THE HON'BLE HIGH COURT OF DELHI, AT NEW DELHI

The Humble Petition of

the Petitioners above-named

MOST RESPECTFULLY SHOWETH: -

1. That the petitioner is filing the instant writ petition in public interest. The petitioner has no personal interest in the litigation and the petition is not guided by self-gain or for gain of any other person / institution / body and that there is no motive other than of public interest in filing the writ petition.

2. That the petitioner has based the instant writ petition from information available in public domain, website of medical journals, correspondence with government departments, and from newspaper reports.

3. That the petition, if allowed, would benefit the citizens of this country. Since these persons are too numerous and have no direct personal interest in the matter, they are unlikely to approach this Hon'ble Court on this issue. Hence the petitioner herein is preferring this PIL.

4. The only affected party by the orders sought in the writ petition would be the Union of India, NTAGI, CMC Vellore who have been made as Respondents and Bharat Biotech. To the best of the knowledge of the petitioner, no other persons / bodies / institutions are likely to be affected by the orders sought in the writ petition.

5. The petitioner has made representations to Mr. Sunil Chandy, Director of CMC Vellore and also the Prime Minister's Office. A copy of his email correspondence between 21.05.2015 and 28.05.2015 with Mr. Sunil Chandy, Director, CMC Vellore is annexed as **Annexure P1**. A copy of the said letter sent to the PMO dated XYZ is annexed as **Annexure P2**.

6. The Petitioner herein is Dr. Jacob Puliyel MD MRCP MPhil. He is a Pediatrician (children's doctor) trained in India and the UK, working at

St. Stephen's Hospital (a charitable institution) in Delhi. He is also a member of the National Technical Advisory Group on Immunization (NTAGI) - the highest advisory board on immunization of the Government of India. The Petitioner is filing the present Writ Petition in public interest on behalf of millions of infants who are likely to be administered this vaccine in the near future and also in his personal capacity as a pediatrician and as member of the NTAGI (National Technical Advisory Group on Immunization).

The petitioner has means to pay the cost, if any, imposed by this Hon'ble Court.

7. The Petitioner had earlier filed the following PILs:-

PILs by Petitioner	Status	Outcome
WPC 13698 of 2009 filed by the Petitioner and others in this Hon'ble Court seeking a rational immunization policy.	Allowed and disposed of	In compliance of the Directions of this Hon'ble Court the Government framed an immunization policy.

THE CASE IN BRIEF

8. In March 2015, the Prime Minister launched Rotavirus vaccine Rotavac, developed by Hyderabad-based Bharat Biotech. The said

vaccine has been ostensibly approved by the government after a clinical trial conducted to gauge its efficacy and safety.

9. The Government has not disclosed complete segregated data from all the centres where this clinical trial was conducted on infants, in violation of ethics of medical research and in violation of the global norms governing clinical trials.

10. Therefore, the Petitioner herein has filed this petition in public interest asking for the disclosure of complete and segregated data for all the centres of this study, as it is on the basis of this data that the vaccine is intended to be taken to Phase IV of the study exposing it to nearly 1,00,000 infants.

11. Concealment of this vital data also does severe injustice to the thousands of infants who participated in this study, the researchers who painstakingly conducted the trials and the medical/scientific community who depend on this vital data in their work.

Background:

12. A vaccine trial is a clinical trial that aims at establishing the safety and efficacy of a vaccine. Clinical evaluation is a critical step to support the approval of vaccines. Clinical trials for vaccines are done to assess them for safety, immunogenicity and efficacy.

13. Department of Biotechnology, Ministry of Science and Technology, Government of India conducted a Phase III randomised,

double-blind, placebo-controlled trial, hereinafter “the clinical trial”, of 116E rotavirus vaccine. The clinical trial took place between 11.03.2011 and 05.11.2013 in Delhi (urban), Pune in Maharashtra (rural) and Vellore in Tamil Nadu (rural and urban). Under this trial, 6719 infants participated. (4532 received vaccine; 2187 were controls). The institutions involved in the study were Society for Applied Studies, Delhi; KEM Hospital Research Centre, Pune; and Christian Medical College (CMC), Vellore. Three doses of the oral vaccine were given to infants at ages 6-7 weeks, 10 weeks and 14 weeks respectively. As per the requirement of compulsory registration of clinical trials in India, the above-mentioned clinical trial was registered with the Clinical Trials Registry.

14. It is submitted that one of the secondary outcomes registered was to look for safety of the vaccine in terms of the number of intussusceptions in the 2-year trial period. Intussusceptions are intestinal obstructions that may need an urgent surgery to prevent death, and diagnosed by ultra sound examination. The trial was to test the risk of this potentially fatal side-effect of the vaccine.

15. In its March 2014 issue, the highly esteemed medical journal *Lancet* published a paper on the results of the said study suggesting the vaccine was safe with an efficacy of 53.6 per cent in first year against severe rotavirus gastroenteritis. Overall results for second year of infant life have been published in the August issue of peer reviewed, scientific, UK medical journal *Vaccine* reporting an efficacy of 48.90 per cent against severe rotavirus gastroenteritis. The study in *Vaccine*

states “decisive assessment of the risk of intussusceptions” has been left to phase IV post-marketing studies. However, neither of these papers provides complete segregated data for different centres of the clinical trial.

16. Doubts about the efficacy and the risk associated with the rotavirus vaccine stem from a paper published in journal *Vaccine* dated August 2014 by John and colleagues. According to selectively published findings of this clinical trial, ultrasound evidence of intussusception was found in 17 who had received the 116E vaccine (3.75/1000 or 37.5/10,000) and in only 6 babies receiving placebo (2.636/1000 or 26.36/10,000). There was an excess of 11 cases of intussusception per 10,000 vaccinated. has had to be This is nearly 70 times higher than the risk of intussusception with the current, internationally licensed vaccine - RotaTeq. It must be pointed out that the risk of intussusceptions with the 116E vaccine is 5 to 10 times higher than with the Rotasheild vaccine which had to be withdrawn from the US market on account of this serious adverse effect. The said paper titled ‘*Active surveillance for intussusception in a phase III efficacy trial of an oral mono-valent rotavirus vaccine in India*’ published in journal *Vaccine* is annexed as **Annexure P3**. (http://www.sciencedirect.com/science/article/pii/S0264410X14004058)

17. Intussusception rates varied in the different regions studied by John and colleagues and were found to be especially high in Vellore. In Vellore it was 581/100,000 child-years and in Delhi it was much lower - 27.7/100,000 child-years. It is submitted that the regional differences in

intussusception rates could mean that it may be more risky to use the 116E rotavirus vaccine in some areas. In this regard there is a need for disclosure of segregated data from Vellore for vaccinated and control where the intussusceptions cases were highest.

18. This data is also important because it could point out if a certain section of the population were more susceptible to adverse effects. However despite several attempts the data is not being shared – this is against the most basic norms of clinical research, which is a cause for great concern.

19. It is submitted that the data was collected in the following format but the same has not been provided for the Vellore limb of the trial.

	Vaccine N= 1000	Placebo N=500
Suspected intussusceptions		
Possible intussusceptions		
Ultrasound evidence of intussusceptions		
Brighton Level 1		
Brighton Level 2		

The present petition is for full disclosure of the safety data in this format.

20. In his capacity as a member of the NTAGI and as a person specializing in immunization and child health, the petitioner made repeated attempts to request the then Director and the Principle Investigator, CMC Vellore, Dr. Gangadeep Kang, with a request to

disclose the data for Vellore limb of the study but the same was neither provided to him as a member of NTAGI nor was the same disclosed to the public.

21. In this regard, the the peer reviewed scientific journal *Vaccine* published a detailed letter dated 06.10.2014 from the petitioner asking for this data to be published but the Principal Investigator has not responded to this scientific appeal either. A copy of the letter of the Petitioner in the esteemed, scientific, UK medical journal 'Vaccine' dated 06.10.2014 is annexed as **Annexure P4. (http://jacob.puliyel.com/download.php?id=356)**

22. As a result of the letter published in the journal 'Vaccine', many newspapers through their science correspondents tried to get the information directly from the Principal Investigator but the figures were not provided.

23. It is submitted that the petitioner has also learned from newspaper reports that, far from providing the figures as sought by various stakeholders and experts, the Government now plans to study the vaccine in 100,000 infants, without providing evidence of safety in the 1000 children already studied in Vellore. A copy of the news report dated 30.3.2015 published in the Hindu is annexed as **Annexure P5**.(http://www.thehindu.com/news/national/other-states/india-to-reevaluate-rotavirus-vaccine/article7046573.ece)

24. On 26.05.2015, the petitioner, with the help of an NGO filed an RTI application seeking information on the number of cases of

intussusceptions in the 1000 infants given the 116 E rotavirus vaccine over the study period of 2 years and what is the corresponding figure for the 500 who were placebo recipients in Vellore limb of study. As it was a matter of the lives of children and as it was anticipated that the Government was to launch the Phase IV trial endangering 100,000 more babies this RTI was filed for a reply within 4 days. No response has been received for the same.

25. The petitioner made a representation to the Director, CMC, Vellore over repeated emails. Initially the Director, CMC, agreed to provide the data, but later sent a reply saying they would not provide the data requested (annexed above as Annexures P1)

26. The petitioner has made representations to the Prime Minister's Office apprising the Prime Minister of the issue and the need for the required data. In his letter the petitioner also made note of the fact that "12 years before the trial was even started – (in 1998) Bill and Melinda Gates Foundation's PATH had already selected the manufacturer for the vaccine – (a pharmaceutical that had no licensed product at all and zero experience with vaccine manufacture)" (annexed above as Annexure P2).

27. In a bid to persuade the Director of CMC Vellore, to release the data, so far 418 people from all over the world have signed a petition to the Director, Christian Medical College, but no response has been received so far. A copy of the online petition is annexed as **Annexure P6.** The online petition can be accessed at: *https://secure.avaaz.org/en/petition/To_The_Director_Christian_Medic*

al_College_Vellore_632004_Release_Indian_Rotavirus_Vaccine_Trial_Data/ .

28. It is submitted that eminent scientist like Dr. Vetury Sitaraman, former head of biotechnology at the University of Pune, has also written personally to the Director Christian Medical College Vellore to provide the data but without success.

29. It is submitted that if the data from Vellore shows that more children who were vaccinated had intussusceptions than the controls in Vellore, it will demonstrate that children in some areas are more susceptible to this potentially fatal side effect. If, in the trial of 1000 children, the risk has already been demonstrated, it becomes unconscionable to do further trials exposing 100,000 children to this risk.

30. However, segregated data for Vellore has not been disclosed despite repeated attempts by the petitioners as well as many in the medical and research community. Non-disclosure of such important data violates the basic ethics of clinical research that require results of clinical research studies to be published and brought to the knowledge of the medical community, participants to the research and general public.

31. On 14.04.2015 the World Health Organization (WHO) released a strong statement advocating public disclosure of all clinical trial results. It argues that when data is not released it means that doctors, patients and medical regulators cannot make informed decisions about which

treatments are best. A copy of the 'WHO Statement on Public Disclosure of Clinical Trial Results' released on 14.04.2015 is annexed as **Annexure P7**.(http://www.who.int/ictrp/results/reporting/en/)

32. The highly cited journal PLoS Medicine elaborates of the reasoning for the WHO Statement. It states " it is unethical to conduct human research without publication and dissemination of the results of that research. In particular, withholding results may subject future volunteers to unnecessary risk." This is annexured (http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001819)

33. It is submitted that when researchers embark on a clinical trial, they make a commitment to conduct the trial and to report the findings in accordance with basic ethical principles. This includes preserving the accuracy of the results and making both positive and negative results publicly available. Selective reporting, regardless of the reason for it, leads to an incomplete and potentially biased view of the trial and its results.

34. Declaration of Helsinki is a highly regarded document providing the ethical guidance on research involving human beings, which has been revised over the years. In the latest version of the Declaration of Helsinki it is stated that *"Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject."* and that *"Researchers have a duty to make publicly available the results of their research...." Negative and inconclusive as well as positive results must be published or otherwise made publicly available".* In other words, there is an ethical imperative to report the results of all clinical trials, including those of unreported

trials conducted in the past. A copy of the World Medical Association's 'Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects' is annexed as **Annexure P8**. (http://www.wma.net/en/30publications/10policies/b3/17c.pdf)

35. It is submitted that complete disclosure of clinical trials of a vaccine such as rotavirus 116E is especially important because the Government of India plans to take the research to Phase IV which will expose approximately another 1,00,000 infants in different regions of the country to this vaccine and its risks.

36. Not reporting complete data for clinical trial results is likely to lead to dissemination bias. This bias has the following major adverse consequences:

- It affects understanding of the scientific state of the art.
- It leads to inefficiencies in resource allocation for both research and development and financing of health interventions.
- It creates indirect costs for public and private entities, including patients themselves, who pay for suboptimal or harmful treatments.
- It potentially distorts regulatory and public health decision-making.

Furthermore, it is unethical to conduct human research without publication and dissemination of the results of that research. In particular, withholding results may subject future volunteers to unnecessary risk.

37. It is important that experts and the medical community is provided with this data urgently before more trials are conducted as this information can be crucial to the lives of the children in the new proposed study.

38. If it becomes apparent to the court that the safety data was deliberately concealed from the public because it shows increased risk in the vaccinated at Vellore, (to protect the interest of vaccine manufacturers,) the court may consider what it must do to prevent such happenings in the future. The Courts and the public repose tremendous faith in scientists making technical decisions. People in Research Organizations, in Government (Ministry of Health - Immunization Division), NTAGI, Drug Controller must all be held responsible, so it does not happen again.

39. The petitioner has not filed any other petition, application, suit, complaint regarding the matter the in dispute before the Hon'ble Supreme Court, or any other High Court or any other court or tribunal throughout the territory of India. The petitioner has no better remedy available.

GROUNDS:

A. Because the respondents have ignored the scientific appeals, RTIs, online appeals of the petitioner and many others who are to gain by this scientific data and have failed to provide the said data which can affect millions of infants in this country.

B. Because, if the data from Vellore shows that more children who were vaccinated had intussusceptions than the controls in

Vellore, it will demonstrate that children in some areas are more susceptible to this potentially fatal side effect. If, in the trial of 1000 children, the risk has already been demonstrated, it becomes unconscionable to do further trials exposing 100,000 children to this risk.

C. Because in the said clinical trial there was an excess of 11 cases of intussusception per 10,000 vaccinated. This is nearly 70 times higher than the risk of intussusception with the current, internationally licensed vaccine - RotaTeq. The risk of intussusceptions with the 116E vaccine is 5 to 10 times higher than with the Rotasheild vaccine which had to be withdrawn from the US market on account of this serious adverse effect.

D. Because non-disclosure of such important data violates the basic ethics of clinical research that require results of clinical research studies to be published and brought to the knowledge of the medical community, participants to the research and general public.

E. Because the World Health Organization (WHO) in April 2014 has released a strong statement advocating for public disclosure of all clinical trial results.

F. Because when data is not released it means that doctors, patients and medical regulators cannot make informed decisions about which treatments are best. Non-disclosure of complete

clinical trial results means that hundreds of thousands of patients have volunteered to take part in clinical trials (risking their lives in the interest of scientific advancement) have been duped, where results have been kept hidden or are only selectively disclosed.

G. Because that when researchers embark on a clinical trial, they make a commitment to conduct the trial and to report the findings in accordance with basic ethical principles. This includes preserving the accuracy of the results and making both positive and negative results publicly available. Selective reporting, regardless of the reason for it, leads to an incomplete and potentially biased view of the trial and its results. Selective reporting of clinical trial results can also lead to wrong or unnecessary allocation of public funds, which could otherwise have been used in public interest.

H. Because the Declaration of Helsinki, an international document providing ethical guidance on research states that *"Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject."* and that *"Researchers have a duty to make publicly available the results of their research .... Negative and inconclusive as well as positive results must be published or otherwise made publicly available".*

I. Because the Government of India plans to take the research to Phase IV which will expose approximately another 1,00,000

infants in different regions of the country to this vaccine. In this regard complete disclosure of clinical trials of a vaccine such as rotavirus 116E is especially important.

J. Because the Courts and the public repose tremendous faith in scientists making technical decisions. People in Research Organizations, in Government (Ministry of Health - Immunization Division), NTAGI, Director General of Cosmetics and Drugs must all be held responsible for non-disclosure of such important data.

PRAYERS:

In view of the facts & circumstances stated above, it is prayed that this Hon'ble Court may be pleased to:

a. Issue an appropriate writ directing the respondents to provide complete segregated data on the clinical trial conducted in all three centres, including the number of intussusceptions (numbers with symptoms of intussusceptions and numbers diagnosed by ultrasound examination) in the 2-year trial with 116E rotavirus vaccine.

b. Issue an appropriate writ restraining the respondents from conducting any further trial of rota virus 116E vaccine in India until complete data from the previous trial is not disclosed to the key stakeholders, including the petitioner.

c. Issue an appropriate writ directing the respondents to frame guidelines regarding publication of complete and segregated

research results in clinical trials on humans, in accordance with the WHO statement of April 2015 on the issue.

d. Issue such other writ, direction or order, which this Hon'ble court may deem fit and proper under the facts and circumstances of the case.

Through

Prashant Bhushan / Neha Rathi
Counsels for the Petitioner

Drawn by: Neha Rathi
Drawn and Filed on:
New Delhi

SYNOPSIS AND LIST OF DATES

The Petitioner has filed this petition in public interest seeking a writ directing the respondents to provide complete segregated data on the clinical trial of rotavirus vaccine 116E conducted by the respondents on infants. The petitioner through this petition is also seeking a writ directing the respondents to frame guidelines regarding compulsory publication of complete and segregated research results in clinical trials on humans, in accordance with the norms of World Health Organization and World Medical Association.

Department of Biotechnology, Ministry of Science and Technology, Government of India conducted a Phase III randomised, double-blind, placebo-controlled trial, hereinafter “the clinical trial”, of 116E rotavirus vaccine. The clinical trial took place between 11.03.2011 and 05.11.2013 in Delhi, Pune and Vellore. Under this trial, 6719 infants were given the vaccine or a placebo (an inert substance).One of the secondary outcomes registered was to look for safety of the vaccine in terms of the number of intussusceptions in the 2-year trial period. Intussusceptions are intestinal obstructions that may need an urgent surgery to prevent death, and diagnosed by ultra sound examination. The trial was to test efficacy of the vaccine and the risk of this potentially fatal side-effect of the vaccine.

Doubts about the efficacy and the risk associated with the rotavirus vaccine emanate from a paper published in journal *Vaccine* dated August 2014 by John and colleagues. It has been found that there was an excess of 11 cases of intussusception per 10,000 vaccinated. This

is nearly 70 times higher than the risk of intussusception with the current, internationally licensed vaccine –RotaTeq). In fact this is 5 to 10 times higher than the risk of intussusception with Rotashield which vaccine had to be withdrawn from the market in the USA because of this adverse effect.

Intussusception rates varied in the different regions studied by John and colleagues and were found to be especially high in Vellore. In Vellore it was 581/100,000 child-years and in Delhi it was much lower - 27.7/100,000 child-years. It is submitted that the regional differences in intussusception rates could mean that it may be more risky to use the 116E rotavirus vaccine in some areas. In this regard there is a need for disclosure of segregated data from Vellore for vaccinated and control where the intussusceptions cases were highest.

However despite several attempts, the complete segregated data from all the centres where this clinical trial was conducted on infants is not being shared, which against the most basic norms of clinical research involving human subjects. This is a cause for great concern. Complete disclosure of clinical trials of a vaccine such as rotavirus 116E is especially important because the Government of India plans to take the research to Phase IV which will expose approximately another 1,00,000 infants to the vaccine in different regions of the country. This data is also important because it could point out if a certain section of the population were more susceptible to adverse effects.

In this regard, the peer reviewed international journal *Vaccine* published a detailed letter dated 06.10.2014 from the petitioner asking

for this data to be published but the Principal Investigator has not responded to this scientific appeal. The petitioner also made representations to the Director, CMC, Vellore and the Prime Minister's Office, however the request for the required data was not acceded to. The medical and research community has also started an online petition with an aim to persuade the Director of CMC Vellore to release the data. However, no response has been received so far.

On 14.04.2015, the World Health Organization (WHO) released a strong statement advocating for public disclosure of all clinical trial results. In the latest version of the Declaration of Helsinki it is stated that *"Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject."* and that *"Researchers have a duty to make publicly available the results of their research...." Negative and inconclusive as well as positive results must be published or otherwise made publicly available".*

If it becomes apparent to the court that the safety data was deliberately concealed from the public because it shows increased risk in the vaccinated at Vellore, (to protect the interest of vaccine manufacturers,) the court may consider what it must do to prevent such happenings in the future. The Courts and the public repose tremendous faith in scientists making technical decisions. People in Research Organizations, in Government (Ministry of Health - Immunization Division), NTAGI, Drug Controller must all be held responsible so it does not happen again.

11.03.2011	Department of Biotechnology, Ministry of Science and Technology, Government of India conducted a Phase III randomised, double-blind, placebo-controlled trial, hereinafter “the clinical trial”, of 116E rotavirus vaccine. The study was conducted at three centres namely Pune, Delhi and Vellore.
October 2013	Revised version of Declaration of Helsinki is adopted which states that *“Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.”* and that *“Researchers have a duty to make publicly available the results of their research...." Negative and inconclusive as well as positive results must be published or otherwise made publicly available”.*
05.11.2013	The above mentioned clinical trial was completed
March 2014	*Lancet* publishes a paper on the said study however the paper did not provide complete segregated data for different centres of the clinical trial.
August 2014	Questions about the efficacy and the risk associated with the rotavirus vaccine emanated from a paper authored by John and colleagues published in journal *Vaccine.*
20 March 2015	The *Vaccine* published a detailed letter dated 06.10.2014 from the petitioner asking for this data to be published but the Principal Investigator has not responded to this scientific appeal.

March 2015	The Prime Minister launched Rotavirus vaccine Rotavac, developed by Hyderabad-based Bharat Biotech. The said vaccine has been ostensibly approved by the government after a clinical trial conducted to gauge its efficacy and safety
30 March 2015	The Hindu published an article stating that the Government now plans to study the vaccine in 100,000 infants, without providing evidence of safety in the 1000 children already studied in Vellore.
14.04.2015	World Health Organization (WHO) released a strong statement advocating for public disclosure of all clinical trial results.
26.05.2015	The petitioner, through a NGO filed an RTI application seeking information on the number of cases of intussusceptions in the 1000 infants given the 116 E rotavirus vaccine over the study period of 2 years and what is the corresponding figure for the 500 who were placebo recipients in Vellore limb of study. As it was anticipated the Government was to launch the Phase IV trial endangering 100,000 more babies this was a matter of the lives of the children, the RTI was filed for a reply within 4 days. No response has been received for the same.
.07.2015	Hence the instant writ petition.

Annexure Letters to Director CMC Vellore

On Thu, May 21, 2015 at 6:22 PM, Puliyel <puliyel@gmail.com> wrote:
Dear Dr Sunil Chandy

Your reply below was forwarded to me. I am sure you meant it when you wrote that you were willing to answer any further queries on this and so this email.

Perhaps you have not seen the letter published in Vaccine asking for the data. For clarity I am attaching the letter published in Vaccine so you will know the context in which your letter was sent to me.

Given that the 'CMC data is clean and gone through several layers of IRB clearances' I feel there must be a misunderstanding about the data requested and that is why it is not provided so far.

The data requested is very simple:

How many cases of intussusception (diagnosed by ultrasound) were there in the 1000 infants given the 116 E rotavirus vaccine over the study period of 2 years and what is the corresponding figure for the 500 who were placebo recipients.

If the data is available you have only to provide those 2 figures and put the controversy to rest.

The Statement from CMC Vellore does not provide this data nor do the papers attached. No matter what you have been told, let me assure you that this data has not been provided to the NTAGI either. I look forward to your response.

Warm regards

Sincerely

Jacob Puliyel

sunil chandy <sunilchandycmc@gmail.com> May 21

Dear Dr Puliyel,

Thank your for your letter and query. I will certainly find out the answers from the PIs of the trial and get back to you. It may take a few days as I am travelling and so is, I understand, the PI. Will get back as soon as possible.

Warm regards

Sincerely

Sunil Chandy

Jacob Puliyel <jacob@puliyel.com> 28 May

Dear Dr Sunil Chandy and others
I am still operating on the premise that I have not communicated my concerns clearly. I feel strongly that all the senior Professors copied in would not be party to concealing data which can potentially harm children.

There are 2 objections being made against providing disaggregated data from Vellore as requested in my Vaccine letter

1. The sample size is not powered to look for intussusceptions

2. The data aggregated from all three centers is provided (as under in blue) and if statistical significance was not seen in this bigger (3 site sample) the chance of statistical significance from the smaller sample in one site is even lower.

This is the aggregated data published from all three centers

According to J John Vaccine 325 (2014) A104-109 data from active surveillance for intussusceptions was performed for 2 years. Aggregated data for the 3 centers has been provided

	Vaccine N= 4532	Placebo N=2267
Suspected intussusceptions	960	472
Possible intussusceptions	914	447
Ultrasound evidence of intussusceptions	17	6
Brighton level 1	5	3
Brighton Level 2	8	3

1. The Power question

Power of study is to be sure that the study does not say there is no difference between groups just because sample size was too small when actually there was a difference - called Type 2 error.
Sample size calculations are done assuming incidence of problem is same as reported in other papers and they want to be sure the study is 'Powered' to avoid type 2 error.

But if incidence is *more* than other places you can show statistical difference with a smaller sample

If statistical difference is shown between groups obviously it is powered adequately.

If the incidence of intussusception is very low you need a very big sample to prevent type 2 error. But in Vellore the incidence was 20 times higher than Delhi and Delhi is much higher than other papers. So with a smaller sample statistical difference will show up.

If statistical difference is shown then it is Powered enough!

2. Can a smaller sample show significance when the larger aggregated analysis showed no statistical significance

It is true that the likelihood of showing statistical significance is more if sample size is bigger and the aggregated 3 site data is ordinarily more likely to show significance and if it is not there, sub group site data is less likely to show difference

BUT this is correct ONLY if the incidence of the incidence of the problem is the same at each site. Say it is 10 in 100 in each site and 30 in 300 combined. 10 in 100 may not be statistically significant but when added up 30 in 300 may show statistical difference. Looking at subset is counter productive in this way.

But now suppose one site has 30 in 100 and other sites are 0 per 100 and 0 per 100(I am taking an extreme case for illustration)
30 per 300 may not be significant but in sub set 30 per 100 will be significant. **Here sub - center analysis may show significance not see earlier.**

We must remember that the incidence of intussusception in Vellore was 20 times higher than Delhi according to the report.
Looking at Vellore alone may show significance but it may be diluted with the low incidence in other areas.

If there is a 20 fold difference between sites it shows that population in Vellore are more susceptible and use of the vaccine in this population may be risky. This is why it is important to put the segregated data from Vellore (in the format of the table above) in the public domain to allay all anxiety.

Looking at incidence in international literature is meaningless when we have just collected our own data in this trial.

I hope that in the interest of scientific transparency the data will be provided.

I look forward to your reply.

Jacob Puliyel

sunil chandy <sunilchandycmc@gmail.com> 28 May

Dear Dr. Puliyel

Your reasoning and interpretation of the data may kindly be directed to Dr Vijayraghavan, Secretary DBT under whose jurisdiction this study was done.

I will also discuss these inferences with the PIs here and revert to you if needed.

Regards

Sunil Chandy

Jacob Puliyel <jacob@puliyel.com> 28 May

Dear Dr Sunil Chandy
You write

I will also discuss these inferences with the PIs here and revert to you if needed.

I will look forward to that. I know people have put RTI with DBT and not been provided the information so far. I can understand that - given that the virus is named after its former DBT chief And they are so invested in it. But for CMC it is just another study which they have to do dispassionately, scientifically, ethically and in Public interest.

I suggest you as head of the institution - and the matter has escalated so far that there are real risks to the reputation and standing of the institution - just look at the data and reassure me that my fears are unfounded, I will be grateful.

Of course that begs the question that if the data were completely innocent why will any one want to conceal it? Can a table of adverse events like in my last letter - but related to intussusception events at Vellore - that shows no statistically meaningful differences be misrepresented and misinterpreted by me and that is the fear of giving the data?

Warm regards

Jacob Puliyel

Letter to PMO

Jacob Puliyel MD MRCP MPhil

Head of Pediatrics, St Stephens Hospital, Delhi.

puliyel@gmail.com

16/06/15

To

The Principal Secretary

Prime Minister's Office

South Block Raisana Hill

New Delhi 110011

Sir

The British Medical Journal last week carried the story of the campaign to release safety data on the 'Indian' Rotavirus Vaccine. This is available here.

http://www.bmj.com/content/350/bmj.h2867/rapid-responses

http://www.bmj.com/content/350/bmj.h2867

It seems the number of potentially fatal side effect (of intestinal obstruction called intussusceptions) was so high in Vellore that the data is not being released but the vaccine has been licensed for general use.

American Vaccine

This is actually an American vaccine and Intellectual Property (IP) rights are held by them. The way international agencies got the Department of Biotechnology (DBT) and MoHFW to get the PM involved, by getting him to inaugurate the vaccine as a 'Make in India' vaccine was devious and unfortunate.

30 years ago a baby passed this virus in its stool and that is the extend of the 'Make in India'.

It was made into a vaccine in the USA and then passed back to India to do the expensive work of testing the vaccine and getting it licensed saying it was an 'Indian' vaccine. Even as the costs were borne by India, the Data Status Monitoring Board (DSMB) for the study was in the USA.

Phase 3 clinical trials were started in 2011. However ***12 years before the trial was even started*** – (in 1998) Bill and Melinda Gates Foundation's PATH had already selected the manufacturer for the vaccine – (a pharmaceutical that had no licensed product at all and zero experience with vaccine manufacture). All this happened many years before 'Make in India' campaign started.

The Government of India was supposed to license the drug and give it as a gift to this private manufacturer. The clinical trial was a mere formality.

The Government should not want to have anything to do with a vaccine that harms children. Now that the international press has got involved the truth will come out eventually.

What can be done now?

The PMO can ask for the figures (asked for in the British Medical Journal, namely how many children developed symptoms of this intestinal obstruction, how many were proved by

ultrasound). If the risk of adverse effects (even symptoms of intestinal obstruction) are significantly more than among controls (simple statistical significance tests) the PMO must ask for temporary revocation of the license. If the vaccine is unsafe in the Vellore population, (even if it is not so dangerous in Delhi,) obviously the vaccine cannot be licensed for general use all over India.

It then needs to enquire about the involvement of the international agencies and collusion with Government (including the Drug Controller who licensed it). The plan for this was made with government connivance, way back in 1998. Continuity in governance policy after government changes is good in principle but this cannot extend to scams that harm children.

I understand the Department of Biotechnology plans to do bigger uncontrolled trials with the vaccine. This will be completely unethical if the risk has already been demonstrated in the randomized control trial in Vellore.

If we do not act now, the excellent scheme 'Make in India' will be drawn into controversy like the controversy about the Lion, and get discredited.

I trust you will enquire into the matter and inform the PM if needed.

Sincerely

Jacob Puliyel

Member of the National Technical Advisory Group on Immunization (GoI)

Copy to

Mr Ajit Doval, National Security Advisor, South Block, Raisana Hill, New Delhi 110011