Does Vitamin A Supplementation Improve Sputum Conversion Among New Sputum Positive Pulmonary Tuberculosis Patients Treated With DOTS Strategy? Mayurbhanj, Orissa 2004-05 – A Pilot Study

A randomised control trial

By

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Dissertation project submitted in partial fulfillment of the requirements for the degree of Master of Applied Epidemiology (M.A.E) of

Sree Chitra Tirunal Institute for Medical Sciences and Technology,
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This work has been done as part of the two year Field Epidemiology Training Programme (FETP) conducted at

National Institute of Epidemiology,
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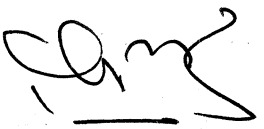
APRIL 2005

CERTIFICATION

This is to certify that this dissertation entitled **"Does vitamin A supplementation improve sputum conversion among new sputum positive pulmonary tuberculosis patients treated with DOTS strategy? Mayurbhanj, Orissa 2004-05 – A pilot study"**, submitted by **Dr. Susanta Kumar Swain** in partial fulfillment of the requirements for the degree of Master of Applied Epidemiology is the original work done by him and has not been submitted earlier in part or whole for any other (Publication or degree) purpose.



Date 01-05-2005

DIRECTOR

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ACKNOWLEDGEMENT

Many dignitaries and institutions have extended their valuable time, advice and assistance to me during preparation of this thesis. I extend with gratitude my sincere thanks to:

Prof. M.D.Gupte, Director National Institute of Epidemiology (NIE), Chennai for his valuable guidance amidst his very tight schedule.

Prof. K. Ramachandran, Formerly Professor and Head of the Department of Biostatistics, All India Institute of Medical Sciences, New Delhi and presently Adviser to DG, ICMR for Field Epidemiology Training Programme at NIE, Chennai for his valuable comments suggestions and advice.

TEPHINET for funding from Micronutrient Malnutrition small project research grant, Division of International Health, CDC, Atlanta GA, USA.

The Principal Secretary to Government of Orissa (Health & Family Welfare) and Director Health Services, Orissa, who have kindly selected me to undergo this course as a Government sponsored candidate.

Dr. Arati Behera, CDMO, Mayurbhanj who facilitated the research works with her excellent managerial and administrative support in Mayurbhanj district.

Dr. Madan Godbole, Prof and HOD Department of Endocrinology, Sanjay Gandhi Memorial Post Graduate Institute of Medical Sciences, Lucknow for laboratory analysis of the Dry Blood Spots for estimation of Serum Retinol.

Dr. (Mrs) Santha Devi, Deputy Director, Sr. Grade and Dr. Kumaraswamy, Deputy Director, Sr. Grade, Tuberculosis Research Centre, Chennai for her guidance in conducting the study.

Dr. T. Venkat Rao, Assistant Director, NIE, for his constant guidance throughout the course as my NIE preceptor.

Dr. Vidya Ramachandran, Assistant Director, NIE and MAE-FETP Course coordinator, for her close guidance and encouragement.

Dr. R. Ramakrishnan, Assistant Director, Dr.P.Manickam Research officer, Dr. Murekar, Deputy Director, FETP, Mr. Sundermurthy, Statistician, Mr. S. Satish, librarian and Uma Manoharan Secretary to the FETP for their constant support and guidance.

My co-investigators: Dr. Satya Ranjan Panigrahi, TB and Chest Diseases Specialist, DHH, Baripada, Dr. Mahendra Nath Das, DTO, Mayurbhanj, Dr. Snigdha Ghana, Pathologist, DHH, Baripada for their hard work.

Dr. Prameela Baral, MO, Regional PH Laboratory, Baripada in compilation and processing the raw data.

All the MO TUs, MO PHIs, STSs, STLSs, LTs and DOTS providers working under RNTCP in Mayurbhanj district and staff of DTC, Baripada those participated in the research activities and made this a success.

Dr. Y Van Hutin, Resident Advisor, FETP-India, WHO, SEAR for able guidance in scientific writing.

Last but not the least all the respondents who very graciously spared me their valuable time and information in addition to extending their cooperation and generous hospitality, which rendered the entire research, endeavor a very memorable, pleasant and profitable experience.

Date: 29/4/05

29/4/05

Dr. Susanta Kumar Swain

ABSTRACT

Introduction: Sputum positive Pulmonary Tuberculosis patients are highly infectious and an infectious (sputum positive) case can infect 10-15 healthy individuals in an average a year. One third of global population is infected with Mycobacterium tuberculosis. Poverty and malnutrition are closely associated with the disease. Vitamin A deficiency is one of the many micronutrient deficiencies prevailing among TB patients. At the end of intensive phase (two months) of Directly Observed Treatment Short course (DOTS) under Revised National Tuberculosis Control Programme (RNTCP) in India 80% of New Sputum Positive cases become negative. Any drug contributing to improve sputum conversion will be beneficial for mankind. .

Goal: To improve sputum conversion of sputum positive cases under DOTS strategy.

Objective: To determine whether patients with vitamin A supplementation have a higher rate of sputum conversion.

Methods: We conducted a randomised placebo control trial in Mayurbhanj district with a calculated sample size of 100 new sputum positive cases in each arm. We estimated baseline serum retinol by HPLC through dry blood spot test and assessed for sputum conversion at one month, 1½ months and two months.

Results: Out of 100 study subjects three in treatment group and four in control group died before completing the study period. Among them 95 became sputum negative with vitamin A and 72 became sputum negative with placebo. Relative Risk 1.29(1.15,CI, 1.45). The proportion of sputum conversion was higher with vitamin A (86.6%) at one month in comparison with placebo group 35.8%. Mean rise in serum retinol after supplementation of vitamin A and placebo were 49.21 and 7.88 µgm/dl, respectively.

Conclusion: Supplementation of vitamin A had significant role in improving the sputum conversion. Rise in serum retinol level was directly proportional to sputum conversion rate with vitamin A supplementation. It is recommended to supplement vitamin A with Directly Observed Treatment Short course strategy under Revised National Tuberculosis Control Programme in India where vitamin A deficiency is prevalent to achieve improved and earlier sputum conversion.

1. Introduction

1.1. Global scenario:

The World Health Organisation considers tuberculosis to be one of the six infectious diseases of poverty that are largely preventable but kills nearly 14 million people every year. Tuberculosis ranks seventh among the leading causes of Disability Adjusted Life Years (DALY) lost and expected to maintain its position up to 2020. (Murray) According to International Federation of Red cross and Red Crescent Societies (IFRC) natural disasters killed 80,000 people last year, while tuberculosis killed two million. Nearly one third of the world's population is infected with Mycobacterium Tuberculosis. From this pool of infection approximately eight million new active infectious cases of tuberculosis occur every year. Someone who develops active tuberculosis infects 10 to 15 persons, on average, in a year. The poor suffers disproportionately from tuberculosis. Tuberculosis both arises from poverty, creates it and worsens it. According to the stop tuberculosis partnership, living conditions that are associated with poverty, including overcrowding, poor ventilation and malnutrition greatly increase an individual's probability to develop active tuberculosis. Tuberculosis attacks people primarily between the ages of 15 and 44, the most economically productive years of life. HIV infected persons are 30 times more likely to develop tuberculosis and become infectious to others. The global TB-AIDS co-epidemic is leading to a major loss of lives in sub-Saharan Africa and South Eastern Asian Region. Poverty, malnutrition and tuberculosis maintain a vicious cycle. Nearly two million lives can be saved with existing effective Directly Observed Treatment Short course (DOTS). The Stop tuberculosis Partnership just established a Global Tuberculosis Drug Facility housed at World Health Organisation to facilitate expansion of access to high quality anti-tuberculosis drugs and Directly Observed Treatment Short course (DOTS) worldwide. More than 150 countries all over world are under the cover of Directly Observed Treatment Short course (DOTS) today.

1.2. Indian scenario:

India accounts for one-third of global burden of tuberculosis.(www.tbcindia.org) It has more tuberculosis cases than any other in the world and twice as many as in China that has the second highest number of cases. About 40% of Indian population is infected with tuberculosis. Everyday in the country 20,000 people become infected and out of the 5000 develop the disease. Every year of 1.8 million Indians developing the disease 0.8 million are sputum positive. Tuberculosis is leading killer of adults in India (>400,000 deaths each year), though being completely curable. It is a major barrier to economic development costing US$ 3 billion a year for India. As it affects most productive age group of population it causes enormous social and economic disruption and development in the country. With an estimated five million HIV positive population in India (NACO), it is likely that HIV may worsen tuberculosis epidemic as 50-60% of them are estimated to develop tuberculosis.[1]

Directly Observed Treatment Short course is an effective anti tuberculosis treatment package that has been progressively covering India phase wise since 1997 following planning in 1993 under Revised National Tuberculosis Control Programme (RNTCP). These Directly Observed Treatment Short course (DOTS) can cure 90% of tuberculosis cases in HIV positives and allow them to live a healthier longer life. The implementation of Revised National Tuberculosis Control Programme (RNTCP) has resulted in net savings of more than US$ 27 billion through 2020 in India (World Health Organisation joint tuberculosis programme review, India, February 2000, New Delhi. India, WHO/SEA/TB/224). The Revised National Tuberculosis Control Programme RNTCP is now covering nearly 8 million people in 431 districts in 27 states and union territories. Directly Observed Treatment Short course (DOTS) under Revised National Tuberculosis Control Programme (RNTCP) is a systematic strategy with five components like political and administrative commitment, good quality diagnosis, good quality drugs, directly observed treatment, as well as systematic monitoring and accountability. In operational research priority has been assigned to achieving cure rate of at least 85% of the registered new smear-positive pulmonary tuberculosis cases and detecting at least 70% of the estimated New Sputum Positive cases existing in the community. The Directly Observed Treatment Short course (DOTS) strategy provides supervised treatment at home that reduces the stigma that is divided into two phases i.e. intensive phase for two months and continuation phase for four months with good quality drugs like Isoniazide, Rifampicin, Pyrazinamide and Ethambutol for new sputum positive cases. India is

achieving its goals well with Revised National Tuberculosis Control Programme (RNTCP) under Directly Observed Treatment Short course (DOTS) a cure rate of 86%, three months sputum conversion rate to new sputum positives is 90% in India.

1.3. State of Orissa:

Mayurbhanj is the northernmost district of Orissa a state on the eastern part of India. This is an economically challanged state (nearly 45% of the population living below poverty line) It is often struck by natural disasters like cyclone, flood and drought. Orissa is the state with highest Infant Mortality Rate (IMR) and prevalence of various problems of malnutrition is high. The magnitude of malnutrition includes protein energy malnutrition (kwasiwoker, stunted growth, marasmus) iron deficiency anaemia, vitamin A deficiency (night blindness, xerophthalmia, bitot's spot etc) and deficiency of other micronutrients like iodine. A study conducted by United Nations Development Project (UNDP) in Orissa indicates that 34% people suffering from iron deficiency anaemia 6% from Vitamin A deficiency (3% with night blindness). Fortunately Mayurbhanj district was covered under Revised National Tuberculosis Control Programme (RNTCP) since 1997 assisted by Denmark. Already seven years have passed since Revised National Tuberculosis Control Programme (RNTCP) covers the district. Achievements have been very nice i.e. the new sputum positive case detection rate (91%), sputum conversion rate (3 months 88%), cure rate (85%) and success rate (87%) have been satisfactory[1]. The Revised National Tuberculosis Control Programme (RNTCP) has set targets based on an epidemiological study conducted by National Tuberculosis Institute, Bangalore, Tuberculosis Research Centre, Chennai, 2000-2003 for case detection rates on the basis of prevalence of infection 6.9% and Acute Respiratory Tract Infection cases by percentage 1.3%(95%Confidence Interval) for east zone[1]. The programme has been successful in achieving stated targets in past seven years. Still more new sputum positive cases nearly 90 per one lakh population) are emerging from the community.

We have not been able to reduce the load of infectious cases from the community. It appears, there is a higher burden of disease (TB) than estimated at national level. However elimination of sputum positive cases from the community can reduce the burden of the disease. As soon as we get a case of sputum positive tuberculosis our foremost aim will be sputum conversion. If a diagnosed sputum positive case of remains active for two moths spreading infections, it may double the cases in the community. Already the Revised National Tuberculosis Programme is achieving high cure

rate. However it would be our interest to make it faster. In order to achieve earlier sputum conversion, drugs and/or micronutrients as adjuvant or supplementation along with DOTS Vitamin A has been used experimentally, with positive effect.

1.4. Background:

Malnutrition is frequently observed among pulmonary TB patients. Several studies report malnutrition indicated by reduction of visceral protein, micronutrient status and anthropometrics indices [27,28]. However nutritional status in respect of vitamin A level is poorly documented. Poor level of dietary intake of retinoids are associated with immuno-suppression may explain the increased risk of infectious diseases in countries with chronic malnutrition[27]. There are studies stating decreased serum level of retinol during TB infection[24,25]. Low plasma level of serum retinol was reported in South African children with pulmonary tuberculosis.[24]. Karyadi et al have reported earlier sputum conversion following vitamin A and zinc supplementation during TB treatment[14]. Deficiency of vitamin A increases bacterial adherence to epithelial wall of respiratory tract[13].

2. Justification of study:

The Revised National Tuberculosis Control Programme has an objective emphasizing the 85% sputum conversion for newly diagnosed smear positive cases of tuberculosis through directly observed short course chemotherapy. Hypothetical adjuvant or supplementation that would help early sputum conversion and reduce the period of intensive phase of chemotherapy instead of prolonging it for one more month as it is happening with 16% new sputum positive TB patients in our field situation in Mayurbhanj district.

Vitamin A is believed to augment the host defense mechanism in two ways. It maintains the integrity of epithelial cells of respiratory and elementary tract[15,16]. During deficiency of vitamin A the pulmonary epithelial cells are keratinised. That increases the adherence of bacteria and lodge easily on the epithelial wall, in absence of mucous secretion by goblet cells in the pulmonary epithelium. Following supplementation of vitamin A the integrity of epithelium and mucous secretion re-establish. Thus the mucous secretion facilitates excretion of bacteria. In the other way supplementation of vitamin A augments the host defense mechanism by strengthening the immune system. Vitamin A and its metabolites are immune enhancers that potentiate antibody responses to T-cell dependent antigens increase lymphocyte proliferation responses to antigens and inhibit apoptosis.

Considering these merits the benefits of supplementation of vitamin A in recommended doses may be determined. Its impact on sputum conversion will be tested.

3. Objective:

3.1. Primary objective:

To determine whether DOTS with vitamin A supplementation have a higher rate of sputum conversion.

3.2. Secondary objective:

Compare the rate of sputum conversion among newly diagnosed sputum positive TB patients with higher and lower retinol level.

4. Literature Review:

4.1. Revised National Tuberculosis Programme in India:

In 1992, after 40 years of organized domestic TB control strategy the Indian government established a Revised National Tuberculosis Programme (RNTCP) using Directly Observed Treatment, Short-course (DOTS) strategy recommended by the world health organization (WHO). In the 1993 the programme was launched as pilot projects in the country. In 1998, large-scale programme implementation followed all over the country. The Revised National Tuberculosis Control Programme was launched in 1997 in Mayurbhanj district of Orissa where the present study was conducted. Three months sputum conversion rate, cure rate and success rate are 90%, 86% and 87% respectively at national level. In Mayurbhanj district, the study area the sputum conversion rate, cure rate and success rate it are 90%, 88% and 89% respectively.[35] Sputum conversion is taken as the prognostic criteria. In Mayurbhanj district 16% of new sputum positive cases remaining positive at the end of two months of intensive phase of short course chemotherapy[35].

4.2. Directly Observed treatment Short course (DOTS) strategy:

Directly Observed treatment Short course (DOTS) strategy is the primary component of Revised National Tuberculosis Control Programme(RNTCP) in India. Laboratory network, good quality of drug and its management, supervised drug compliance, in programme evaluation; quality control by National Tuberculosis Institute, Bangalore and Tuberculosis Research Centre, Chennai. Accuracy of diagnosis of TB is twice that of other diagnostic methods. The case fatality ratio of new smear positive cases with DOTS is 4% in where as it is 29% in absence of Directly Observed treatment Short course.[1]

4.3. Vitamin A and its deficiency:

Vitamin A has two protective features to support immune defense system of humans. First it helps in maintaining the integrity of epithelium of lungs and intestine. The goblet cells in the lining epithelium of lungs secrete mucous to keep it moist and to protect against invasion of bacteria by reducing their adherence. During vitamin A deficiency the lungs epithelium gets keartinised. Absence of secretion of mucous also reduces the protective capability of lungs epithelium. Ten

days after vitamin A supplementation the epithelial tissue regenerates and secretion resumes providing a protective layer to lungs.

Vitamin A, the fat-soluble vitamin is absorbed on the brush borders of small intestine and stored in fatty tissues of the body and liver as carotenoids. Cholestasis or steatorrhoea reduce the absorption of caretinoid or pro-vitamin. Retinol Binding Protein (RBP) transports it. Free RBP in blood suggests a deficient state of vitamin A. During severe malnutrition when protein content is depleted free RBP is not available even if there is vitamin A deficiency. Usually vitamin A is not excreted through urine. During acute infections urinary excretion of vitamin A along with other antioxidants are observed. Some believe that during acute infections concentration of some protein increase where as some protein decrease. Retinol Binding Protein decreases during acute infections while vitamin A absorption and transportation fails to occur. After the acute infectious phase is over the RBP as well as vitamin A normalizes.

Infectious diseases depress circulating retinol and contribute to vitamin A depletion. Enteric infections may alter absorptive surface area, compete for binding sites and increase urinary loss. Measles viral infection is devastating to vitamin A metabolism, adversely interfering with both efficiency of utilization and conservation. Severe protein energy malnutrition affects many aspects of vitamin A metabolism and even some store of retinyl ester is present, malnutrition coupled with infection can prevent transportation by preventing transport protein synthesis. The result is immobilization of vitamin A stores.

For estimating the levels of retinol level in urine the unit of measurement is retinol equivalent that is conventionally used. The unit expressed such is clarified in a conversion table below.

Units of measurement:

1 RE = 1mcg of Retinol

1RE = 6 mcg of beta carotene

1 RE = 3.333 UI of vitamin A

(By Joint FAO/WHO Expert group in 1967)

Daily requirement of vitamin A for human consumption by age and sex is described below.

Daily recommended intake of vitamin A:

Table.1: Recommended RE per day

Individuals	RE per day
Babies 0-1 yr	350
Children 1-3 yrs	400
Children 4-6 yrs	450
Children 7- 9 yrs	500
Children 10-12 yrs	550
Children 13-15 teenager	700
Teenager girl 13-15	600
Teenager boy 16-19	800
Teenager girl 16-19	600
Men	800
Women	600
Pregnant women	700
Nursing mother	950

Recommended Dietary Allowance (RDA) by Laurence LIVERNANS-SAETEL, Dietician

Source website: Ma Ville on line

Table. 2 : Estimated mean requirement and safe level of intake for vitamin A

Age group	Mean requirement µgm per day	Recommended safe intake µgm per day
Infant and children		
0-6 months	180	375
7-12 months	190	400
1-3 years	200	400
4-6years	200	450
7years	250	500
Adolescents,10-18years	330-400	600
Adult		
Females-19-65 years	270	500
Males-19-65 years	300	600
65+	300	600
Pregnant woman	370	800
Lactating woman	450	850

Sources: Adapted from FAO/WHO 1988 (69)

Vitamin A supplementation may be encountered with toxicity. To prevent toxicity the maximum limit of recommended doses are stated in the Table.2. Described above.

Table.3: Available supply of vitamin A by WHO region

Region	Total mg RE/day	Animal sources mg RE/day	Vegetable sources mg RE/day
Africa	775	122	654 (84)
America	814	295	519 (64)
South East Asia	431	53	378 (90)
Europe	738	271	467 (63)
Eastern Mediterranean	936	345	591 (63)
Western Pacific	997	216	565 (72)
Total	782	212	565 (72)

Numbers in parentheses indicate the percent of total retinol equivalents from carotenoid food sources
Sources: ACC/SCN, 1993(76)

4.4. Vitamin A deficiency and TB:

It has been documented in several articles with supportive evidence of anthropometrics measures and reduction in visceral proteins.(Guwaheliti J.K. in Eu journal of Nutri., 1988) Several studies state decreased vitamin A in serum. Patients weighing less than 35 kgs are at 4 times risk of dying than those weigh >35kgs though mortality among smear positive cases is 4%[29,30]. Vitamin A deficiency has been reported in children with pulmonary TB in South Africa[21].Mugusi F.M. stated vitamin A deficiency is problem among the persons with HIV and TB infection particularly in those who are affected by both.

Vitamin A supplementation to TB patients can modulate immune response and can reduce morbidity and mortality. [16] (Semba R.D., 1994)

Studies in Rwanda, Tanzania, South Africa, Indonesia and South India also reported significantly lower vitamin A level during infectious state of TB[19].South Indian study by Ramchandran et al. stated that the serum retinol level returned to normal after anti TB treatment was over without supplementation of vitamin A[36].

Karyadi et al. in Indonesia have reported earlier sputum conversion following supplementation of vitamin A and zinc with anti TB drugs[21]. They also observed early improvement of radiographic abnormalities and gain in body weight. Micronutrient supplementation resulted in an earlier elimination of tubercle bacilli from sputum. Tubercle bacilli were cleared from the sputum within two weeks of initiation of treatment in 23% of patients in study group compared with 13% patients in the control group. The researchers observed that the resolution of lesions as seen in chest x-ray was also faster in the group with micronutrient-supplementation.

Supplementation of vitamin A in Tanzania to children less than five years (2,00,000 IU every six months) for two years consecutively reportedly reduced mortality due to TB in that age group by 25%.[22]

Supplementation of vitamin A to children has reportedly reduced the mortality due to measles and diarrhoeal diseases but not from pneumonia in children living in developing countries.[4]

5. Methods

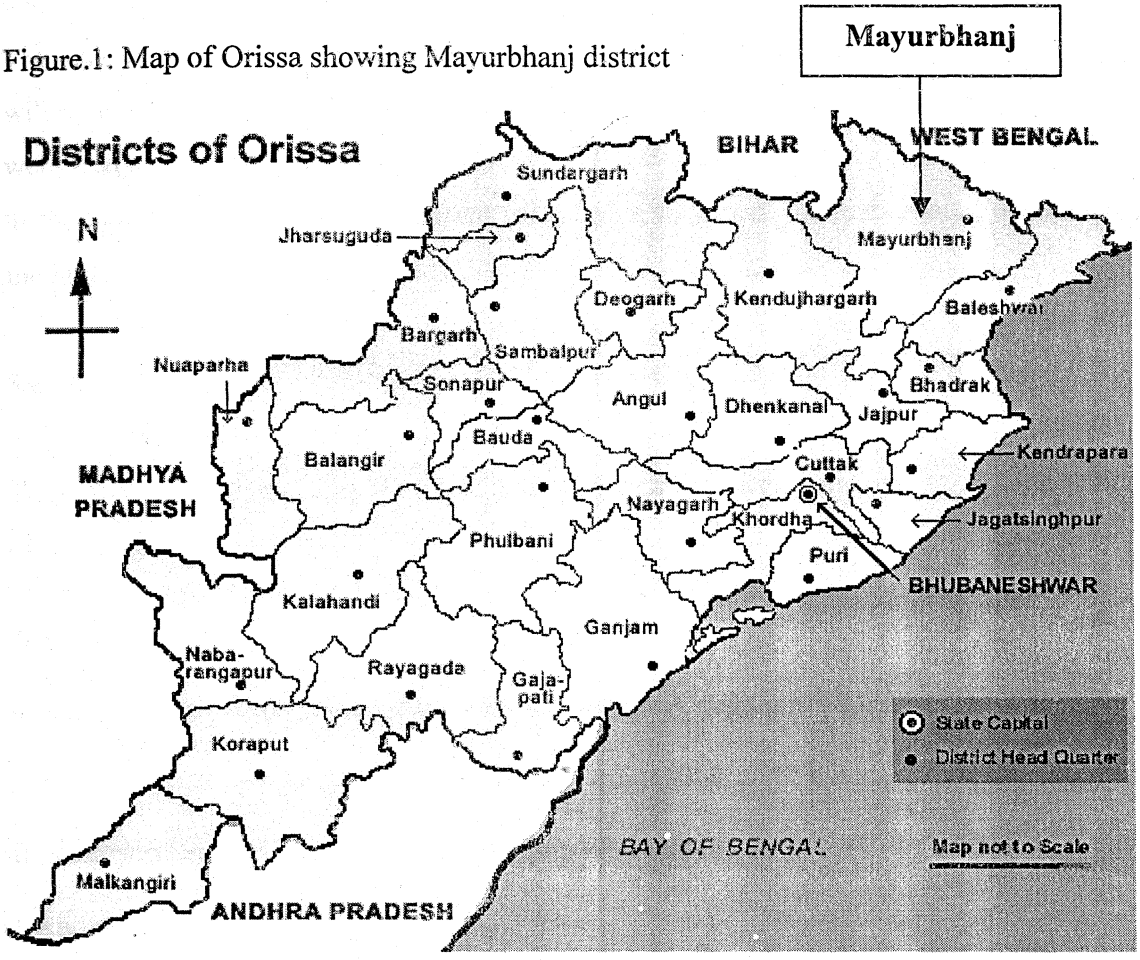
5.1. Study design:

Randomised, double blind placebo control trial

5.2. Study area:

Mayurbhanj district in Orissa , India

Figure.1: Map of Orissa showing Mayurbhanj district



Mayurbahnj district is the northern most district of Orissa sharing two interstate borders with Jharkhand and West Bengal. It has got a geographical area of 10,418 sqr. Kms.with central 405 covered with monsoon deciduous forest. A total of population 23, 12, 695 (2004 midyear population) live in the district (60% tribal)

5.3.Study population:

Defined the study population as the population residing in Mayurbhanj district. Any resident of the district fulfilling the inclusion criteria had an equal chance to participate in the study.

5.4.Study period:

We conducted the study from October 2004 to February 2005.

5.5. Investigating team:

The investigating team submitted a written informed consent form, expressing voluntary willingness to take part in the study as an investigator. All the members of the investigating team were free to express his/her opinion and leave the study at any stage of the study with information to the investigating team. The consent form had a statement for maintaining transparency among the investigators.

5.6. Sample size:

To estimate the sample size, for a randomized, placebo control, trial the study dealt with sample of two proportions.

Assumption:

i. Sputum conversion in the group without Vitamin A supplementation in directly observed treatment(DOTS) programme after eight weeks 70%

ii. Expected sputum conversion in the group with vitamin A supplementation after eight weeks 90%

iii. Confidence level 95%

iv. Power 90%

$$n = 2 (Z\alpha + Z\beta) \{ P1\ Q1 + P2\ Q2 \} / (P1 - P2)^2$$

Source: Hosmer & Lemshow "Sample size determination"

P1 = 70% = 0.7, P2 = 90% = 0.9

Q1 = 1 – P1 = 1 - 0.7 = 0.3 & Q2 = 1-P2 = 1-0.9 = 0.1

(Given Zα = 1.96 & Zβ = 1.64 "z" value in two tailed table)

$= 2(1.96+1.64)^2 \{ (0.7 \times 0.3) + (0.9 + 0.1)\} / (- 0.2)^2$

$= 2 (3.6)^2 (0.21+0.09) / 0.04$

$= 2 \times (3.6)^2 \times 0.3 / 0.04$

$= 7.776 / 0.04$

$= 194.4$ say 195

Then the sample size on each arm was 97.5 rounded up 98 and total trial size was 196

Total trial size = 196 say 200 new sputum positive TB patients

So the required sample size was 200 patients i.e. 100 patient in each arm of the trial.

Calculation of sample size by Epi 6:

Assumption:

i) Sputum conversion in the group without Vitamin A supplementation in DOTS programme after 2 months - 70%

ii) Expected sputum conversion in the group with Vitamin A supplementation - 90%

Confidence level - 95%

Power – 90%

Then the sample size of each arm will be 92 and total size will be 184

Including follow up losses made it 200

Total Trial Size – 200 (100 in each arm including follow up losses)

5.7. Randomization:

The principal Investigator randomized study subjects to receive vitamin A or placebo and maintained the registers. The method of block randomization was used to have equal number of patients in each arm (one arm with anti tuberculosis drugs +vitamin A and the other with anti tuberculosis drugs + Placebo) at any given point of time. Since the required sample size was 200,

and we have to reach the target sample size from 34 peripheral health institutions of six patients each were prepared in advance. Two blocks are given below as an example. Assign Vitamin A for Random Nos.0-2 and Placebo for Random Nos. 3-5. The random numbers i.e 0,1,2,34,5 were allocated from random number table given in a standard Bio-statistics book.

Block – 1

S.No.	R.Nos.	Treatment
1	0	Vitamin A + TB drug
2	3	Placebo + TB drug
3	4	Placebo + TB drug
4	5	Placebo + TB drug
5	1	Vitamin A + TB drug
6	2	Vitamin A + TB drug

Block - 2

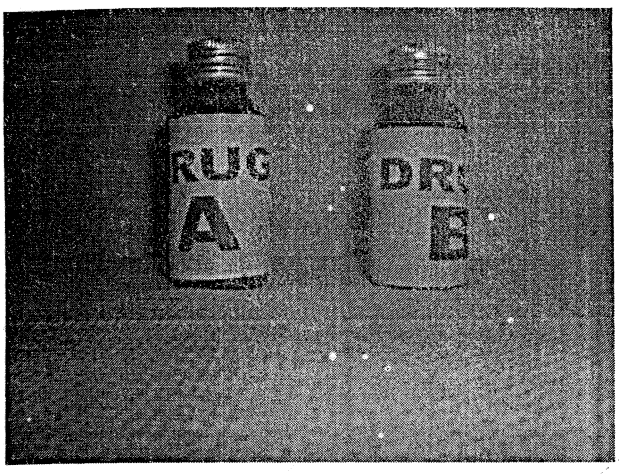
S.No.	R.Nos.	Treatment
7	3	Placebo + TB drug
8	4	Placebo + TB drug
9	2	Vitamin A + TB drug
10	5	Placebo + TB drug
11	0	Vitamin A + TB drug
12	1	Vitamin A + TB drug

The study we conducted in 34 sputum microscopy centers of the district. Each microscopy center had to include 6 study subject in average. We allotted one identification (ID) number to each study subject that was entered into a master register kept with the principal investigator. The principal investigator had to allot an ID number and one randomization number to each new study subject recruited. We allocated of the study subjects into experimental and control group that was confidential.

5.8. Blinding:

We packed sealed and labeled the vitamin A and the placebo – Glycerine as Drug-A and Drug- B respectively. The bottles for packing Drug –A and Drug – B appeared identical.

Figure.2: Sample of intervention drugs Vitamin A and placebo packed and labeled as Drug A and Drug B in identical bottles for blinding



None was aware of the drug in each bottle. A secret code was maintained in a register that was decoded after the study period was over. The provider as well as the study subject who was receiving the intervention drugs either A or B was kept blind about the type of drug being supplemented. The drug allocated by random table number was dispensed to the study subject. The study subject was receiving the supplementary drug in addition to anti TB drugs under DOTS in presence of the provider at the sputum microscopy center.

5.9.Inclusion Criteria:

Any resident of Mayurbhanj found out to be new smear positive, without history of anti-TB drugs in the sputum microscopy center under RNTCP, willing to receive DOTS is included in the study.

5.10.Exclusion Criteria:

Anybody qualifying the inclusion criteria of a study subject but with diabetes, history of hepatitis, bony injury, pregnancy and seriously ill persons (un-ambulatory) were not excluded in study. Any body with previous history of adverse reactions to vitamin A and anti-TB drugs were not included. As vitamin A is contraindicated in the above said condition we did not want to put them under supplementation for ethical values.

5.11.Selection of a study subject:

The selection of the study subject for inclusion in the study was based on voluntary participation of the subject. The Medical Officer of the peripheral health institution, treatment units and other centers working for RNTCP and providing DOTS did the selection.

5.12. Training of the manpower

We trained the medical officers and the laboratory assistants working in sputum microscopy centres during a half-day training with working lunch about the details of the study and its procedures. The tuberculosis and chest diseases specialist, pathologist and qualified laboratory technicians were trainers there. We trained them about the use of study instrument, consent form and record keeping.

5.13. Procurement of drugs

The intervention drugs like Vitamin A and glycerin had identical packing in 100 ml packing for each sputum microscopy centre. The drug logistics and the questionnaire with recording registers and informed consent forms were provided to the sputum microscopy centres separately.

5.13.a) Quality control:

We sent samples of the drugs procured to two different laboratories for quality control.

5.14.Consent:

We all took written informed consent from the subjects before including them in study. The written informed consent form was written in local language keeping all ethical issues in mind.

5.15. Laboratory investigations:

The staff working under RNTCP conducted the sputum examinations. Preserved the slides for internal and external quality control Sputum examination. Randomly selected sputum samples for cross-examined by the pathologist in the investigation team by choosing random number of slides. Collected blood for estimation of serum retinol as Dry Blood Spot samples. We used the filter papers from Molecular diagnostic laboratory, Lucknow for collecting three samples for each subject. The laboratory performed the tests by High Performance Liquid Chromatograohy (HPLC) were considered as the report. For each study subject, we collected the sample twice. In each sitting we collected three blood spots after getting written informed consent from the participant. Each filter paper with dry blood spots were preserved and transported to Molecular Diagnostic Laboratory, Lucknow covering it with black paper and protecting it from sunlight in freezing temperature as sunlight degrades the retinol during transportation.

5.15.a). Quality control:

For internal quality control three serum samples were tested in three separate sittings and the pooled value of these three observations was the result. For external quality control some randomly selected samples were tested in three different laboratories.

5.16. Ethical issues:

Before the outset of the study the Institutional review board of National Institute of Epidemiology, Chennai reviewed the project proposal and approved it after revision[32]. The participation of the subject in study was completely voluntary. The subject had freedom to withdraw (her) himself from the study at any point of the study. Non-participation in the study did not deprive nay subject from getting benefits of Directly Observed Treatment Short course under Revised National Tuberculosis Control Programme. We maintained confidentiality of the participation and the results of the study and laboratory investigations there of. There was no physical or psychological risk to the subjects included. The little physical risk of pricking for dry blood spot was taken care of by maintaining asepsis. If supplementation of vitamin A is proved beneficial to tuberculosis patients, that can be of great contribution to human beings. All the subjects in the study under

placebo and vitamin A had a scope for free family health check up and advise by a team of physician, gynecologist, pediatrician and surgeon. They also received free treatment and drugs for any health problem during the study period.

5.17. Implementation:

Using the pre-developed study questionnaire (Annexure-1) the detailed information about the patient was taken. After obtaining informed written consent from the willing participant, (s) he was included in the study as per inclusion criteria. Allocation of study subjects to vitamin A and placebo at sputum microscopy centres was predetermined following the flow of the table stated in randomisation section earlier. Intervention drug was allocated as randomised table number. We gave vitamin A to the subjects with random numbers 0,1 and 2 Glycerine to the random numbers 3,4and 5. The dose of vitamin A given was 2,00,000 IU i.e. 2ml of vitamin A solution with the help of the measuring spoon given with the bottle. The placebo group received the same amount i.e. 2 ml of Glycerine. Trained laboratory technicians took blood samples in three spots on the specified filter paper supplied. The samples collected were labeled and stored in dry and cold place in freezing temperature protecting from sun by wrapping them with black envelope till transportation. During the transportation to the laboratory for analysis care was taken to protect it from sun and heat that may degrade the retinol content of the blood spot. In the questionnaire there was space to record grade of sputum, body weight, drug compliance, outcome of sputum conversion, serum retinol values of both the time i.e. pre and post experiment for each study subject. Maintained record about any withdrawal, drop out and adverse reactions of the study. At the outset of the study the subjects received supplementary drug only once. We examined sputum samples at intervals of one month, 1½ months and two months. Body weight was measured twice, at 0 month and at two months.

5.18. Outcomes:

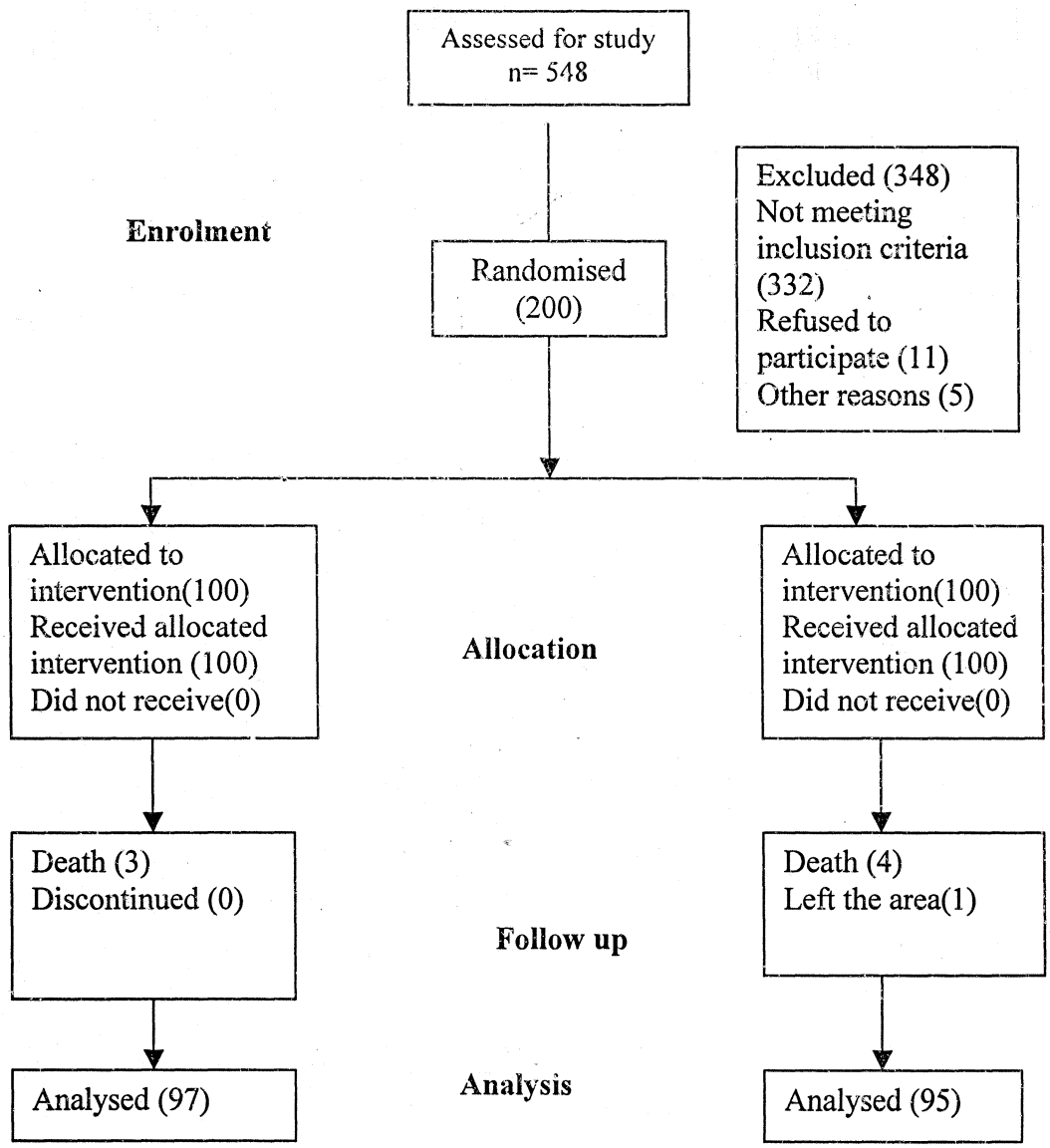
Outcomes of the study regarding sputum conversion, change in serum retinol value, body weight, death, dropouts, withdrawal and adverse reactions were recorded.

6. Result:

6.1. Flow chart of the study subjects:

In the peripheral health institutions, treatment units and district tuberculosis units the pulmonary tuberculosis case-patients were assessed for inclusion in the study. On the basis of new sputum positivity the subjects were enrolled after written informed consent.

Figure.3: Flow chart of study subjects since enrollment till completion of study



Flow diagram of the progress through phases of randomised trial

6.2. Recruitment:

Recruitment and follow up was a continuous process. We spent 75 days from October to mid-December 2004 to recruit the estimated sample size of 200 (100) in each allocation arm. In the study 151 males and 41 females participated. Out of 548 subjects assessed, 332 were sputum negative pulmonary tuberculosis case-patients.

Table.4: Age characteristics of study subjects by sex for vitamin A supplementation study, Mayurbhanj, Orissa, 2004-05

Age	Male (n-151)	Female (n-41)
Minimum	13	16
Maximum	75	65
Median	43	35
Mean	42	37
Standard Deviation	11.74	13.61

After recruitment we followed the study subjects for two months at the intervals of 1 month, 1 ½ months, and two months for examining sputum samples. We examined them for taking body weight and dry blood spots for estimation of serum retinol at the end of two months. During the follow up three subjects from allocation group A and four subjects from allocation group B died out before completing the study period of two months. One from allocation group B left the area of residence could not be traced till the end of study period. At the end we evaluated in the analysis 97 subjects with vitamin A and 95 subjects with Placebo.

6.3. Laboratory Investigations:

The Molecular Diagnostic laboratory at Lucknow performed the analysis of Dry Blood Spots for serum retinol by High Performance Liquid Chromatography (HPLC) under standardized conditions. Each subject gave had received two pricks for giving blood samples twice i.e once at the inclusion and again after two months of the experiment started (at the end of study period). We maintained cold chain in freezing temperature to transport, store and preserve the dry blood spots. Every time the laboratory had to standardize the control run on the HPLC. For each sample (pre and post experiment) we had prepared three blood spots on the filter paper supplied. The laboratory examined three blood spots for each sample in three different settings. Average of three

observations was the estimated serum retinol value of that sample. Like this we examined all the samples take before and after the experiment.

6.4. Baseline data:

Table.5. Comparison of study subjects placed in vitamin A supplementation and placebo groups, Mayurbhanj 2004-05

Parameter	Vitamin A		Control	
	Male	Female	Male	Female
Sex	78 (97)	19 (97)	73 (95)	22 (95)
Age	Mean-42.71 Median-45	Mean-40.57 Median-40	Mean- 42.95 Median-42	Mean-33.68 Median-31
Body weight in kgs	Mean-39.89 Median-41	Mean-33.31 Median-32	Mean-40.22 Median-41	Mean33.22 Median-32
Baseline serum retinol in µgm/dl	Mean-19.01 Median-18.10	Mean-21.92 Median-21.16	Mean-18.10 Median-15.38	Mean-21.16 Median-14.58
Grade of sputum positivity	Scanty-3 (+) - 27 (++) - 29 (+++) - 19	Scanty-1 (+) - 8 (++) - 6 (+++) - 4	Scanty-1 (+) - 35 (++) - 24 (+++) - 13	Scanty-1 (+) - 8 (++) - 9 (+++) - 4

Table.6.Grade of sputum positivity and baseline serum retinol among the study subjects of vitamin A supplementation with DOTS strategy, Mayurbhanj, Orissa 2004-05

Grade of sputum positivity	Vitamin A		Control	
	No of subjects	Level of serum retinol in µgm/dl	No of subjects	Level of serum retinol in µgm/dl
Scanty	4	Mean-11.60 Median- 12.92	2	Mean-21.72 Median- 21.72
+	35	Mean-16.70 Median- 112.70	43	Mean-17.15 Median-12.88
++	35	Mean-18.60 Median- 17.12	33	Mean-22.81 Median- 23.57
+++	23	Mean-17.53 Median- 16.50	17	Mean-19.79 Median-19.37
Total	97		95	

Depending upon the grade of sputum positivity the baseline serum retinol level did not vary proportionately.

While comparing both the vitamin A and placebo intervention groups we found that they were approximately identical on the basis of sex, age, body weight, baseline retinol and grade of sputum positivity.

Table.7: Serum retinol base values and changes after supplementation of vitamin A and Placebo study subjects (by HPLC), Mayurbhanj 2004-05 (n-192)

Values of	Experimental group with Vitamin A (97)			Experimental group with Placebo (95)		
serum retinol	Pre Exp.	Post Exp.	Change	Pre Exp.	Post Exp.	Change
Mean	17.37	66.58	49.21	19.68	27.57	7.88
Median	15.13	69.13	47.73	19.30	28.9	5.74

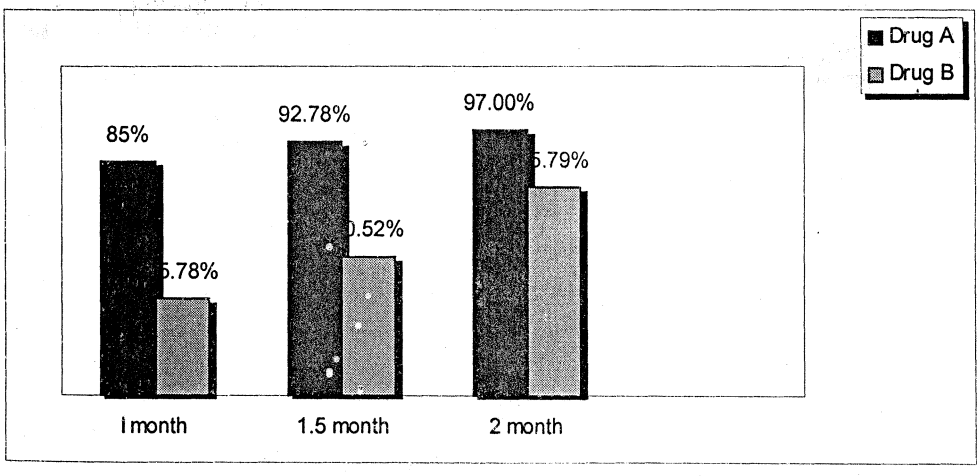
Normal range of serum retinol Adults >12 yrs of age 30-70µgm/dl

6.5. Outcome and estimation:

Table.8. Status of sputum conversion with Vitamin A and Placebo supplementation at different time interval

Sputum conversion	Vitamin A	Placebo	Total
1 month	84	34	118
1 ½ months	94	45	139
2 months	95	72	167
Non-conversion after 2 months	2	23	25
Total	97	95	192

Figure.4: Comparison of sputum conversion proportion with DOTS strategy supplemented with Vitamin A and placebo, Mayurbhanj, Orissa, India 2004-05



Out of 97 new sputum positive subjects followed up till the completion of study allocated in group with supplementation of the experimental drug vitamin A. 84 (86%) at the end 1 month, 10 (10.3%) at the end of 1 ½ months and 1 (1%) at the end of 2 months had their sputum conversion. Only 2 (2.1%) did not have sputum conversion even at the end of 2 months. Out of 95 new sputum positive subjects put under supplementation of placebo – Glycerine, 34 (35.8%) at the end of 1 month, 11 (11.6%) at the end of 1 ½ months and 27 (28.4%) a the end of 2 months had their sputum conversion. Total 23 (24.2%) did not have their sputum converted even after 2 months.

6.5.1. Outcome of sputum conversion:

Table.9: Sputum conversion status with Vitamin A and placebo among study subject, Mayurbhanj, Orissa , India 2004-05 (n-192)

Sputum Conversion at 2 months	Yes	No	Total
Vitamin A	95	2	97
Placebo	72	23	95
Total	167	25	192

Relative Risk- 1.29 (1.15, 95% CI, 1.45)
Chi Square: 18.88 (p value 0.00001)

The study subjects with supplementation of Vitamin A along with DOTS had better sputum conversion than the subjects with placebo along with DOTS. This was statistically significant.

6.5.1.1. Stratification by level of serum retinol:

The median base-line serum retinol level of the study of both the group of study subjects was 17.155 µgm / dl. Taking this as mid point any value above it was considered as high serum retinol and any value bellow it was treated as low serum retinol. The analysis is stated in Table. 9 given bellow.

Table.10. Effect of vitamin A and placebo supplementation on sputum conversion stratified by levels of serum retinol, age, sex and body weight among study subjects (192), Mayurbhanj, Orissa 2004-05

Stratify by	Strata	Vitamin A			Placebo			RR	Adjusted RR(MH)
		n	Total	%	n	Total	%		
Serum Retinol	>17.155µgm/dl	43	44	97	44	53	83	1.18 (1.03, 1.4)	1.31 (1.16,1.48)
	<17.155µgm/dl	52	53	98	28	42	66	1.47 (1.2,1.8)	
Age	40+	58	59	98	45	59	76	1.29 (1.11, 1.49)	1.29 (1.15,1.45)
	<40	37	38	97	27	36	75	1.30 (1.07,1.58)	
Sex	M	77	78	98	56	73	76	1.29 (1.13,1.46)	1.29 (1.15,1.45)
	F	18	19	94	16	22	72	1.30 (0.99,1.72)	
Body weight	+39kgs	48	48	100	39	48	81	1.23 (1.07,1.12)	1.29 (1.15,1.45)
	<39kgs	47	49	96	33	47	70	1.37 (1.12,1.66)	
Grade of sputum positivity	Scanty	4	4	100	1	2	50	2.00 (0.50-7.99)	1.30 (1.15-1.46)
	(+)	34	35	97	34	43	79	1.22 (1.08-74.98)	
	(++)	35	35	100	25	33	76	1.32 (1.08-1.60)	
	(+++)	22	23	95	34	40	85	1.35 (0.98-1.86)	
								Crude RR was 1.29(1.15, CI, 1.45)	

MH -Mantel Hanszel,

All the cut off values for stratification into two groups is by choosing the median of the parameters The subjects supplemented with vitamin A had better sputum conversion rate in both higher and lower serum retinol group. Supplementation of vitamin A benefited the low serum retinol group better. Those supplemented with placebo had better outcome in high serum retinol group. The Relative Risk in low and high serum retinol group were different from each other i.e. 1.18 and

1.47 respectively. The level of baseline serum retinol was an effect modifier that was statistically significant.

6.5.1.2. Stratification by Age:

The median age in all the study subjects was 40 years. Taking 40 years as cut off line we set them in two groups for stratification. The effect of Vitamin A on sputum conversion is represented in both the stratified groups are stated in the table.9. The age had no role like effect modifier or confounder.

6.5.1.3. Stratification by sex:

No significant difference was between sexes. As smaller number of female subjects was there, among them there was a difference in Relative Risk between two stratified groups. In Orissa in RNTCP the new TB case detection rate is one third in females than that among males.

6.5.1.4. Stratification by body weight:

Taking the median body weight for both the groups i.e.39 kgs two groups we prepared two stratified groups for examining the results. We didn't find baseline body weight as a definite effect modifier and confounder.

6.5.1.5. Stratification by grade of sputum positivity:

No confounding was noticed with grades of sputum conversion. Only the numbers of study subjects with sputum positivity graded as scanty were outliers and had Relative Risk 2.0 (0.50-7.99). But the adjusted Relative Risk(Mantel Hanszel) was equal to the crude Relative Risk.

6.5.2. Change in body weight:

All most all the subjects gained body weight in both the groups. The median gain in body weight in vitamin A group was 3kg (mean-2.89, range- 0-6kgs) in comparison with placebo group i.e. 1.0 kg (mean-1.63, range- 3-6 kgs).

6.5.3. Adverse reactions:

We didn't notice any significant adverse reaction during the study period to any supplemented drug. The investigators did not find any adverse reaction in any study subject throughout the study period of two months and till reporting the results.

6.5.4. Effect on mortality:

Among all, seven study subjects died. The Case Fatality Ratio of TB patients put under DOTS strategy is normally 4%. Three study subjects died in Vitamin A group, four study subjects died in placebo group and one left the study area.

7.Discussion:

7.1. Interpretation:

We found from the present study that sputum conversion rate has improved with supplementation of Vitamin A along with DOTS strategy (22% better than placebo supplemented group). In addition to increase in rate of sputum conversion speed of sputum conversion was better. Vitamin A group had earlier sputum conversion i.e 86.6% at the end of one month in comparison with 35.85% in placebo group.

Stratification by high and low level of baseline serum retinol level shows that those with low serum retinol baseline value have benefited much from the intervention of vitamin A. The association of vitamin A supplementation with higher rate of sputum conversion was stronger among this low baseline group than baseline group. TB patients with vitamin A deficiency will be benefited more with the supplementation of Vitamin A. All the age groups were benefited from the supplementation. Both the sexes had increased sputum conversion with vitamin A supplementation. Stratification by baseline body weight had no difference in association of vitamin A supplementation with sputum conversion.

Post experimental serum samples had higher serum retinol level than baseline samples of the same subjects. The placebo-supplemented group also has gained a median rise of serum retinol level by 5.74 µgm/dl. It is much higher (47.73µgm/dl) with vitamin A supplemented group.

Gain in body weight was not so significant after two months of anti TB treatment and supplementation of vitamin A. Though the vitamin A supplemented group had median rise in body weight by three kgs. in comparison with one kg median rise in placebo group.
Vitamin A supplementation had no effect to prevent death due to pulmonary TB. Usually death of PTB cases under DOTS is restricted to 4% where as with other regimen it is reported to be around 29%. Already there were seven deaths among 200 newly diagnosed sputum positive cases.

7.2. Internal validity:

A well structure national programme RNTCP supported the present study. The infrastructure of the RNTCP has its own quality control and evaluation facilities. The programme is already in force since last seven years in the study area.

Sputum examination is the key function of the whole programme. Categorization, prognosis and follow up are based on sputum examination reports. The sputum microscopy centres have got a very sophisticated illuminated microscope and the laboratory technicians are competent enough to conduct the sputum examination under regular supervision of Sector level technicians, Medical Officer, Peripheral Health Institutions and Medical Officer, Treatment Units. The laboratory technicians maintain a sputum examination register and code the slides for future record. However for the present study there were special instructions to preserve the slides until the study was over. Random samples of sputum examined are routinely cross-examined at the department of TB and Chest diseases of Sri Ram Chandra Medical College, Cuttack, Orissa. Weight was taken in spring balance supplied to each sputum microscopy centres to measure the weight for calculating the dosage of anti-TB drugs under DOTS. The quality of anti TB drug supplied under DOTS is beyond doubt and the local drug controlling authority is working to look after that. Micronutrient laboratory at Molecular Diagnostic Laboratory, Lucknow had processed dry blood spot samples by High Performance Liquid Chromatography (HPLC). The result was derived from average of three spots collected on the filter paper. For quality control random dry blood spots were examined in three different sitting in three different days.

Randomisation and blinding helped to reduce the bias of allocating study subjected under chosen supplementary drug category that was strictly followed by the providers under supervision of the investigators and supervisors utilized in the study. The principal investigator did not know about the type of drug dispensed to the study subjects in the peripheral health institutions. We used a coding method that was decoded after the study was over.

The utilization of single large dose of vitamin A supplemented may not be proper and may be influenced by physiological condition of the study subject. The condition of the elementary tract, any diseased condition there may hamper absorption of vitamin A. Availability of the carrier protein, Retinol Binding Protein (RBP) depends upon the nutritional level of the subject. Subjects with malnutrition may not have circulating RBP transport and utilise the vitamin A supplemented. During acute illness liver diseases or diseases of gall bladder reduces utilization of vitamin A supplemented. Absence of dietary fat may reduce utilization of vitamin a supplemented.

7.3. Representativeness:

Study with randomisation takes care of biases. Every subject has equal chance be in either group of intervention. As the study was geographically limited to one district the study subjects will represent the situation and population of the same district. As RNTCP is delivering DOTS through public health institutions the patients attending private sector hospitals for treatment may be missed out. However as the laboratory diagnosis, drugs and follow up are free all most all the TB patients come to public sector for treatment of TB. This may not represent the patients taking other regimen. The current study is examining the effect of vitamin A supplementation in patients with DOTS strategy only. For the patients under DOTS strategy the subject included in the study is a true representative of this part of India. This place in Orissa may have higher level of vitamin A deficiency as described in United Nations Development Project report discussed in literature review section of the article. We have excluded seriously ill patients, diabetics, cases with previous histories of hepatitis to avoid risk that may influence the Representativeness of the study. All the new sputum positive cases may not be turning up to treatment in the geographical area of the study. Passive surveillance may not support representativeness of TB cases. For being a study truly representative active surveillance of cases is recommended.

7.4. Generalisability:

This was a pilot study designed. There is need of similar studies in different geographical conditions and different nutritional backgrounds. The study area is having very good parameters of sputum conversion with DOTS earlier to this interventional study. For making a programme under Directly Observed Treatment Short course (DOTS) successful satisfactory drug compliance is necessary. Here in the study both the placebo and experimental drug had very nice drug compliance (100%). The study was limited for a period of two months. There is a seasonal variation of incidences of chest symptomatic reporting the hospitals.

Directly Observed Treatment Short course (DOTS) is delivered at home. The nutritional background and dietary pattern of individuals are not known and cannot be monitored. The dietary pattern and nutritional background may influence the study. In the current prospective study it was not possible to restrict the subject from taking the supplementation of any other multivitamin or drugs or special kind of food. Though the programme instructs every subject under DOTS there is no recommendation for special kind of diet when a patient is ill. Still then it was not possible to restrict them from taking any other adjuvant that may confound.

However another study in Indonesia have supported early sputum conversion with supplementation of vitamin A. A large-scale pilot study with a study period of more than one year may add to generalisabity of the study.

8.Conclusion:

8.1. Effect of Vitamin A supplementation:

8.1.1. Sputum Conversion:

8.1.1.a). Rate of sputum conversion:

Vitamin A supplementation had significantly high association with higher sputum conversion i.e. 97% compared with those supplemented with placebo 75% at the end of two months of intensive phase of DOTS under RNTCP. It was 22% higher than placebo group with DOTS. The Relative Risk was quite significant 1.29 (1.15, 95% Confidence Interval, 1.45)

8.1.1.b). Speed of sputum conversion:

With supplementation of vitamin A Sputum conversion even occurred much earlier than those with placebo i.e. at one month 86.6% of vitamin A group in comparison with 35.8% of placebo group.

8.1.2.Change in serum retinol level:

Subjects in the group supplemented with vitamin A had a raised level of serum retinol after experiment. Even the groups supplemented with placebo had gained a rise in serum retinol.

8.1.3.Gain in body weight:

Both the groups had gained some body weight. The vitamin A group had 3kgs of median rise in body weight, whereas the placebo group had 1kg of median rise in body weight. Mean gain in body weight was 2.89 with vitamin A and 1.63 with placebo.

8.1.4.Rise in serum retinol level:

The median rise in serum retinol level after supplementation of vitamin A was 47.73µgm/dl. Median rise in serum retinol level with placebo supplementation was 5.74µgm/dl that was significantly low. The median value of serum retinol in vitamin A supplemented group was 69.13µgm/dl during post experiment period. At the same time the placebo supplemented group had median serum retinol level as 28.9µgm/dl.

8.1.5.Correlation of serum retinol level and sputum conversion:

Rise in serum retinol level was directly proportional with rate of sputum conversion. The group with higher median level of serum retinol i.e. vitamin A supplementation group had higher rate of sputum conversion. Even sputum conversion was earlier with vitamin A supplementation (86.6% in one month with vitamin A).

9. Recommendations:

Basing on the evidence from the current study we can recommend supplementation of micronutrient: vitamin A to improve sputum conversion rate with DOTS strategy in Orissa where prevalence of vitamin a deficiency is high. That needs to be taken up with meticulous monitoring and evaluation.

Need to conduct further studies in areas with low prevalence of vitamin A to evaluate the idea of supplementation of vitamin A in improving sputum conversion rates.

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NATIONAL INSTITUTE OF EPIDEMIOLOGY

INDIAN COUNCIL FOR MEDICAL RESEARCH
CHENNAI – 31, INDIA

Questionnaire for Patients included under the Pilot study of Vitamin A Supplementation with DOTs strategy of RNTCP

1. Name of the respondent –
2. Age –
3. Sex –
4. Name of the Father / Natural Guardian –
5. Village –
6. Block –
7. PHI –
8. Treatment Unit –
9. Patient Code No –
   (For use by the research workers only) | | | |

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10. Have you been explained about the consent form? | Y | N |

11. Willing to take part in study: | Y | N |

12. Filled up the consent form: | Y | N |

13. History of illness:

Fever	Yes		No	
Cough	Productive		Dry	
Chest pain	Yes		No	
Breathlessness	Yes		No	
Blood in Sputum	Yes		No	
Mobility	Ambulatory		Bed-ridden	

14. History of any other disease (Identified earlier):

Diabetes		Jaundice	
HIV		Pregnancy	
Seriously ill		Others (Specify)	

15. Whether sputum was examined - | Y | N |

16. Result of Sputum examination:

1st visit		2nd Visit		3rd Visit		Remark
Positive	Negative	Positive	Negative	Positive	Negative	

Mention the grades of sputum positives from scanty, (+), (++) & (+++)

17. Laboratory investigation results:

Lab reports	Outset of Intensive phase	End of Intensive phase	Remarks
Serum Retinol (in mcg/dl)			

18. Doses of RNTCP drug and intervention drug taken;

Weeks	1	2	3	4	5	6	7	8	9	10	11	12
Anti-TB Drug												
Weeks	13	14	15	16	17	18	19	20	21	22	23	24
Anti-TB Drug												

Mention the details of the patient (Discontinuation / Drop out / Death / Migration/ Adverse reaction / Others)

19. Intervention drug given on registration

Y	N

20. Completed the scheduled intensive phase:

Y	N

21. Cause of drop out from the study:

22. Suggestions by the respondent:

23. Any adverse reaction observed during the study and steps taken:

Signature of the field investigator
Name and designation

NATIONAL INSTITUTE OF EPIDEMIOLOGY,
CHETPET, CHENNAI -31, INDIA

CONSENT FORM

Name of the Respondent:
Name of Father / Natural Guardian:
(A must in case of minors)
Patient identification Number:
Village:
Block:
Treatment unit:
Date of Registration:

I, Dr. Susanta Kumar Swain, FETP-MAE Scholar of National Institute of Epidemiology, Chennai, India am conducting a research *on "Does vitamin a supplementation improve sputum conversion among newly diagnosed sputum positive cases treated with dots strategy? – a pilot study"* that is a collaborative approach of National Institute of Epidemiology, Chennai, India and TEPHINET, CDC, Atlanta, GA, USA.

Purpose of study:

The study is contemplated as a collaborative effort of National Institute of Epidemiology (ICMR), Chennai and Training in Epidemiology and Public Health Networking (TEPHINET), Center for Disease Control (CDC), Atlanta, GA, and USA. The goal of the study is to improve / enhance the cure rate of Sputum positive TB patients in DOTs programme. For this the objectives set by the study method are: To study the effect of Vitamin A supplementation as an adjuvant with Anti Tubercular drugs under Revised National Tuberculosis Control Programme (RNTCP) and to estimate the level of Serum Retinol at the outset and after 8 weeks of intensive phase chemotherapy under DOTs along with supplementation of Vitamin A to the experimental group and placebo (Antacids) to the control group.

Procedure:

If you agree to participate in the study after fulfilling the inclusion criteria of being found as a New Sputum Positive TB patient you will be explained about the procedure of the study, purpose of the study at the sputum microscopy center that may take 10 minutes by a pre-trained research co-worker. If you volunteer to take part in the study that may be of a great benefit to the TB patients undergoing long-term chemotherapy you will be included under the study. The chances of being included either under placebo or under the drug expected to be beneficial is equal and that will be provided along with scheduled DOTs at the time of registration as a new case. None of them is having any adverse or toxic effect over human body. As a requirement of study, a trained Pathology Technician will take a drop of blood after taking your consent, for Serum Retinol estimation (by dry Blood Spot test) for assessment of your nutritional status. This procedure will be repeated once again after 8 weeks of completion of your intensive phase of DOTs.

Voluntary:

The participation in the study is completely voluntary and you have the option of exercising your freedom to withdraw yourself at any stage of the study. Non-participation in the study will never make you deprived of any facilities available under the RNTCP.

Risk:

There is no physical or psychological risk to the patient. The patient may complain of physical pain while pricking the finger for dry blood spot test. That will be taken care by utilizing trained pathology technician who is an expert in taking samples and maintains the asepsis while pricking.

Benefits:

Your participation may help in planning for supplementation of Vitamin A along with RNTCP drugs to enhance and improve Sputum Conversion. If the participant wants to know the results of the laboratory investigations, it will be made available to him / her free of cost.

If you agree to participate in the study without being under any compulsion, you may please put your signature / Left Thumb Impression in the place mentioned.

Name of the respondent

Signature / LTI of the respondent

Name of the interviewer

Signature of the interviewer

Place –

Date –

Received a Xerox copy of the consent form, duly filled up by me in presence of the interviewer and the witness.

Witness –

Signature / LTI of respondent

Name –

Address –

Place -

Date –