EURECA

Vitamin A Supplementation for Prophylaxis or Therapy in Childhood Pneumonia:
A Systematic Review of Randomized Controlled Trials

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RELEVANCE

Several reports have suggested benefit of vitamin A supplementation in measles, diarrhea, pneumonia, as well as reduction in childhood mortality(1). Although a 2000 WHO review concluded that there is no benefit in pneumonia(2), the current WHO position is that "the official guidelines need to be revised using current evidence"(3).

This systematic review attempts to plug the gap in current evidence by addressing two distinct clinical questions: (*i*) Does community-based vitamin A supplementation in children prevent the occurrence of pneumonia and/or its complications? and (*ii*) Does addition of vitamin A to standard therapeutic protocols improve the clinical outcome in childhood (community acquired) pneumonia? The relevant outcomes for the latter include cure rate, severity, duration, and complications of pneumonia; and adverse events following supplementation.

CURRENT BEST EVIDENCE

The Cochrane Library was searched with the term "*vitamin A*" and filter "*Record Title*" yielding 12 Cochrane Systematic Reviews, 50 other (systematic) Reviews, and 1547 Clinical Trials. Narrowing the search to *'pneumonia'* and *'respiratory infection'* yielded 2 Cochrane Reviews, 2 other Reviews, and 31 Clinical Trials. Simultaneous Medline search for randomized controlled trials yielded the following results: *"(vitamin A) AND pneumonia"* (25 citations), *"(Vitamin A) AND (respiratory infection)"* (62 citations), *"(vitamin A) AND (lower respiratory)" (*32 citations*)*. A total of 41 trials were excluded for the following reasons: (*i*) recruited children with pre-existing pneumonia for further prophylaxis (*n*=3), (*ii*) included children with pre-existing illness (*n*=13), (*iii*) recruited specific participant sub-groups(*n*=9), (*iv*) evaluated a respiratory outcome not consistent with pneumonia (*n*=11), (*v)* did not describe a comparator group (*n*=5). Eleven trials exploring prophylactic role of vitamin A, and 9 trials examining therapeutic role were included in this review. ***Tables*** **I** and **II** summarize the characteristics of the included trials. Hand-searching of the bibliography of included trials identified several potential citations, but no additional trials could be included.

There were two relevant Cochrane reviews on vitamin A, one evaluating vitamin A supplementation for prophylaxis(4) and the other for therapy(5). The prophylaxis review(4) included 9 trials; of these 3 are not justifiable – 2 recruited children with pneumonia rather than community-based children, and one measured respiratory outcomes not consistent with the definition of pneumonia. It is surprising that 5 relevant trials included in this EURECA systematic review (6,7,10,11,16) were not included in the Cochrane review. The therapy review(5) included 6 trials including two Chinese language trials. Besides the 4 English language trials, an additional 5 trials have been included here; 4 of these were inappropriately excluded from the Cochrane review(19,22,24,25) and one(23) was (inexplicably)

TABLE I SUMMARY OF RCTS EXAMINING VITAMIN A SUPPLEMENTATION FOR PROPHYLAXIS OF CHILDHOOD PNEUMONIA

Setting (reference)	Participants	Study design	N(Vitamin A / placebo)	Dose and duration	Follow-up	Outcomes
South Africa, 1993-94(6)	LBW infants (950-1700g)	DB, PC, RCT	56/60	25000U x 3 doses	12 mo	LRTI* Side effects M
Nepal, 1989(7)	< 59 mo	RCT	8/8 districts 3786/3411	200000U**	5 mo	P*, M
India, NS(8)	12-60 mo with acute diarrhea. Excl: W/H<70%	DB, PC, RCT	900 rand omized; 422/420 analyzed	200000U	90 d	P*
Ecuador, 1996-97(9)	6-36 mo	DB, PC, RCT	200/200	10000/wk x 40 doses	DS#	ALRI*
India, NS(10)	< 10 y	RCT	756/759	200000U** x 2-3 doses at 4-6 mo intervals	15 mo	P*, M (P), M (all), diarrhea
Bangladesh, 1997-98(11)	12-35 mo Excl: W/A<60%	DB, PC, RCT	400/200 (200only Vit A & 200 Vit A + zinc)	200000	6 mo	ALRI*, severe ALRI*** (incidence & prevalence)
Indonesia, NS(12)	6-47 mo Excl: W/H<-3sd	DB, PC, RCT	518/518****	206000U** x 6 doses over 2 yr	DS#	ALRI*
Ghana, 1989-91(13)	6-11 mo	DB, PC, RCT	92/93 clusters*****	200000U** x 6 doses over 24 mo	DS#	M (all), M (ALRI) death, hospitalization, clinic attendance
Brazil, 1990-91(14)	6-48 mo Excl: W/A<60%	DB, PC, RCT	620/620	200000U** x 3 doses over 12 mo	DS#	ALRI* CXR P
India, NS(15)	6-60 mo	RCT	7764/7764	2500mcg/wk x 52 wk	DS#	LRI*
Indonesia, 1992-93(16)	newborn	RCT	1034/1033	52 micromol	12 mo	M (all), M (P), various ARI symptoms

*ALRI = acute lower respiratory infection; CXR = chest radiograph consistent with pneumonia; DS# = Follow-up was carried out until supplementation was continued; LBW = low birth weight; LRTI = lower respiratory tract infection; NS = not specified; P = pneumonia; * Study definition consistent with WHO pneumonia; ** Infants less than 12 months received half this dose of Vitamin A; *** Study definition consistent with WHO severe pneumonia; **** This trial described 1036 eligible children randomized in a 1:1 allocation ratio; ***** Number of participants in each group not described clearly.*

TABLE II: SUMMARY OF RCTS EXAMINING THERAPEUTIC ROLE OF VITAMIN A SUPPLEMENTATION IN CHILDHOOD PNEUMONIA

Setting (reference)	Participants	Study design	Definition used	N(Vitamin A / placebo)	Dose and duration	Outcomes
Ecuador, 2002-04(17)	2-59 mo, W/A <50th ct *n*=287 Excl: sev. UW, wasting	DB, PC, RCT	P * = Clinical +CXRClinical = tachypnea, fever, cough or ID, hypoxemia, and 1 of 4 ausc. signs	145/142	100,000U**	Duration of tachypnea, fever, hypoxemia, all three
Peru, 1994-95(18)	3mo-10y Excl: W/H <70th ct	DB, PC, RCT	P* = multiple clinical signs + CXR	47/49	200,000 U followed by 100,000U**	12 clinical indicators including clinical severity score (8 criteria), need for oxygen, ausc. signs, 6 CXR signs
Vietnam, 1991-93(19)	1-59 mo Excl: W/A<60%	DB, PC, RCT	P = WHO criteria	280/312	200,000U** (2 doses)	Normalization of symptoms (fever, tachypnea), Time to discharge
Brazil, 1994-95(20)	6-59 mo	DB, PC, RCT	P* = fever, tachypnea, dyspnea, ausc. signs + CXR	239/233	200,000U** (2 doses)	Mortality, duration of illness, Complications, Hospitalization of out-patients, Change of antibiotics, adverse reactions
Tanzania, 1993-97(21)	6-60 mo Excl: W/A<60%	DB, PC, RCT	P* = cough + >1 of tachypnea, ID, poor feeding, ausc signs	346/341	200,000U** (2 doses)	Mortality, LOS, duration of symptoms
Mozambique, 1995-97(22)	6-72 mo Excl: marasmus, kwashiorkor	DB, PC, RCT	P* = cough, fever, tachypnea + crepts/bronchial breathing	76/102	200,000U**	Mortality, LOS complications, follow-up at 6 wk for hospit-alization, symptoms
Australia, 2001-02(23)	<11y, indigenous population	PC, RCT	ALRI* = tachypnea + fever/ID or CXR	108/107	200,000U** (2 doses)	Duration of symptoms, LOS, readmission at 120 days
Guatemala, 1991-93(24)	3-48 mo Excl: W/H<70%	DB, PC, RCT	P* = cough $\pm$ tachypnea + breathing difficulty + difficulty eating + cyanosis	132/131	200,000U**	Clinical score, respiratory rate, temperature, saturation, LOS, complications, readmission
India, 1997-98(25)	2-24 mo	DB, PC, RCT	P = WHO criteria, included children had severe pneumonia as per WHO criteria	38/38	100,000U** (4 doses)	Time to resolution of illness, mortality, complications, antibiotic change, adverse effects

** Definition is consistent with WHO definition of pneumonia/severe pneumonia; ** Infants less than 12 months received half this dose of Vitamin A. ausc. signs = asucultatory signs; ct = centile; CXR = chest radiograph consistent with pneumonia; DB = double blinded; Excl = excluded; ID = indrawing; LOS = length of stay in hospital; mo = months; P = pneumonia; PC = placebo controlled; RCT = randomized controlled trial; sev = severe; tachy = tacypnea; UW = underweight; W/A = weight for age; W/H = weight for height; y = years.*

not identified at all. Thus neither Cochrane review can be considered the best evidence on the subject.

From the prophylaxis trials, data for four outcomes could be subjected to meta-analysis *viz*. number of children with pneumonia (***Figure* 1**), incidence per person-time, pneumonia mortality and all-cause mortality. There was no difference between vitamin A and placebo for any of the outcomes. Data for five outcomes from the treatment trials could be subject to meta-analysis viz. Mortality (***Figure* 2**), duration of hospitalization, duration of illness, complications and side effects. Here also, vitamin A did not perform better than placebo. One trial each reported absence of cure and hospitalization among out-patients; the results for vitamin A were similar to placebo. ***Table* III** presents a summary of the results

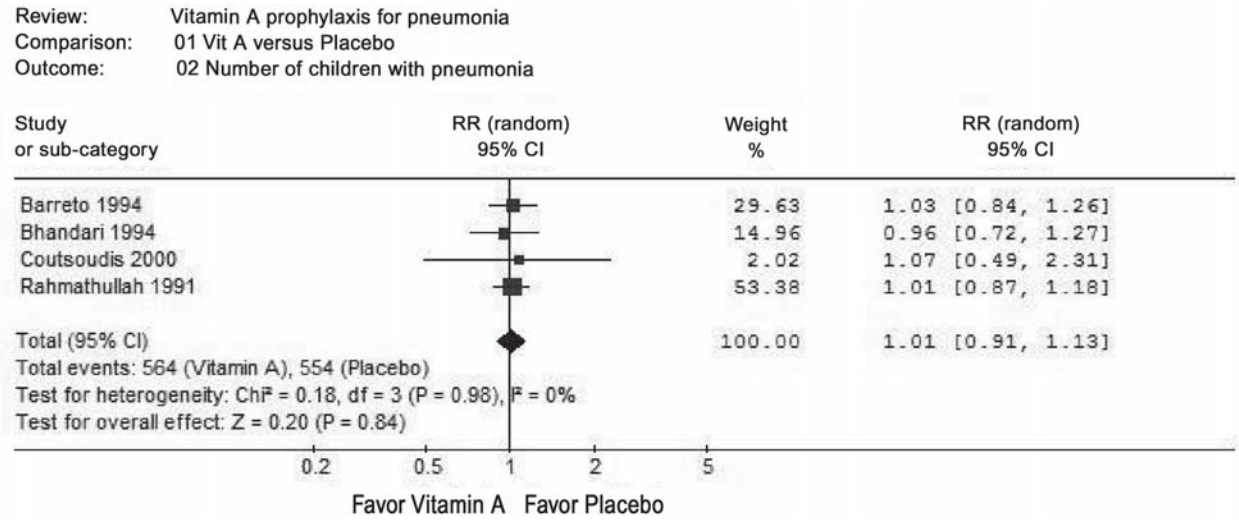

Fig. 1 *Meta-analysis of data reflecting children with pneumonia in prophylaxis trials.*

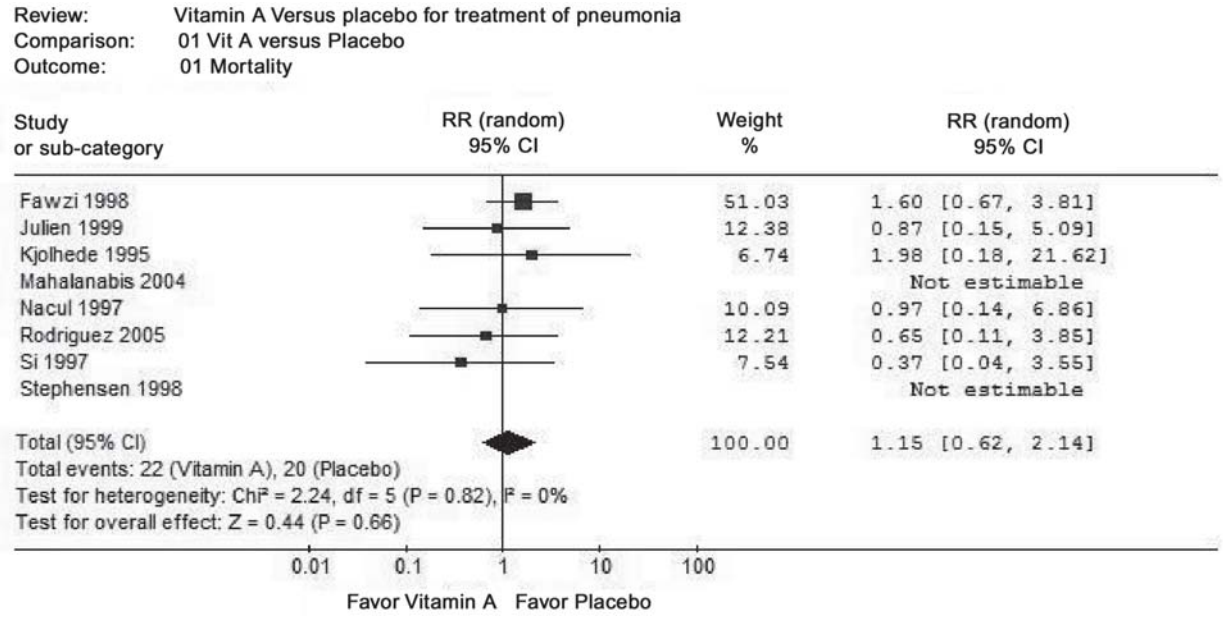

Fig. 2 *Meta-analysis of data reflecting mortality in therapy trials.*

TABLE III SUMMARY OF RESULTS OF META-ANALYSIS

No.	Outcome	Trials (*n*)	Participants (*n*)	Effect size (95% CI)	I^2 (%)
Prophylaxis Trials					
1	Children with pneumonia	4	17577	RR 1.01 (0.91 to 1.89)	0
2	Incidence of pneumonia	5	6337	Rate ratio 1.23 (0.23 to 6.50)	0
3	Pneumonia mortality	2	8595	RR 1.02 (0.55 to 1.89)	0
4	All cause mortality	4	10199	RR 0.50 (0.23 to 1.11)	65.6
Therapy Trials					
1	Mortality	8	2637	RR 1.15 (0.62 to 2.14)	0
2	Duration of hospitalization	2	950	WMD 0.04 (-0.44 to 0.52)	0
3	Duration of illness	2	335	WMD -0.27 (-1.12 to 0.58)	0
4	Complications	4	975	RR 0.77 (0.45 to 1.31)	0
5	Side effects	2	548	RR 1.79 (0.21 to 15.28)	61.1
6	Absence of cure	1	97	RR 1.04 (0.07 to 16.19)	–
7	Hospitalization of out-patients	1	213	RR 2.39 (0.77 to 7.37)	–

RR = risk ratio; WMD = weight mean difference.

of this systematic review and meta-analysis (random effects model). These data suggest that vitamin A supplementation has neither prophylactic nor therapeutic benefit for childhood pneumonia.

CRITICAL APPRAISAL

The 20 trials included in the two components of this systematic review comprise current best evidence from published literature. However, only 1 of the 9 prophylaxis trials could be classified as having low risk of bias(11), while 6(6,7,10,14,15,16) had high risk of bias owing to inadequacies in two or more of the following components: randomization, allocation concealment, blinding, incomplete outcome reporting, and selective outcome reporting. Five trials used serial doses of vitamin A/ placebo, but did not carry out follow-up beyond the period of supplementation(9,12-15). Two trials did not specify the sample size, necessitating indirect calculations(12,13). Two trials did not use definitions of pneumonia consistent with the WHO definition, but contributed data on mortality(13,16).

Seven of the nine therapy trials could be categorized as having low risk of bias(18-20,22, 24-25); two trials(17,21) had missing components affecting the quality grading. A variety of outcomes were measured in these trials, from which some data could be extracted for meta-analysis.

Some trials undertaking post-hoc sub-group analysis suggest that vitamin A could be beneficial in children with pre-existing vitamin A deficiency (determined by low serum retinol) and/or severe malnourished status. There is also data suggesting that supplementation could harm those with adequate baseline levels of serum retinol. This coupled with the fact that children with biochemical deficiency cannot be identified clinically; suggest that the first observation has little practical application. Since only 4 of 11 prophylaxis trials and 2 of 9 therapy trials did not exclude severely malnourished children, data on the second observation is too limited to draw definite conclusions. Therefore, neither issue has been explored further in this EURECA.

EXTENDIBILITY

All the included trials were conducted in developing country populations; the lone developed country trial included Australian indigenous children. The fact that 5 prophylaxis trials and 1 therapy trial were conducted in the Indian sub-continent strengthens confidence in extendibility and applicability of the findings that vitamin A supplementation has no role from the perspective of childhood pneumonia.

EURECA CONCLUSION IN THE INDIAN CONTEXT

- There is neither therapeutic nor prophylactic benefit of vitamin A supplementation for childhood community acquired pneumonia.

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