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Vitamin D Deficiency and Potentially Modifiable Respiratory Morbidity and Mortality among Children: Food for Thought

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Abstract

Background: Vitamin D is known to bear protective effect in prevention and therapy of several childhood systemic morbidities. With a null hypothesis of the positive impact of Vitamin D supplementation among children with Recurrent Respiratory Infections (RRIs) and chronic cough, the present study was planned especially in view of the fact that not many similar studies, systematic reviews or Meta analyses have been affected towards this pursuit.

Methods: A total of 104 children aged between 6 months and 14 years presenting to the Pediatric Outpatient department with recurrent respiratory infections and chronic cough were recruited for this hospital based prospective interventional study planned over duration of 2 years (2016-2018). Vitamin D assay was done in all the candidate children and those with deficient/insufficient levels were given appropriate oral supplementation. Further, these children were followed at 3 monthly intervals up to duration of 12 months for change in respiratory symptomatology, particularly with a view towards reduction in episodes/severity of chest infections and attainment of linear growth.

Results: A total of 104 patients were analysed, of whom 44 patients had a diagnosis of RRI and 60 patients were in the chronic cough group. Serum Vitamin D levels were found to be low in 64% of patients with RRI and 70% of chronic cough patients. There was a statistically significant decline in the number of episodes of RRI and Chronic cough after supplementation ($p<0.05$). In the RRI category, none of the children had enough recurrences to be labeled as RRI after Vitamin D supplementation when followed up to 12 months. In chronic cough patients belonging to Vitamin D deficient subgroup as well, there was a statistically significant decline in the recurrence of cough during a follow up of 12 months ($p<0.05$).

Conclusion: RRIs and Chronic cough along with hypovitaminosis D are significant preventable public health problems in paediatric population. Majority of patients of RRI and Chronic cough have Vitamin D deficiency. Screening for Vitamin D among 'at risk' children and subsequent supplementation thereof even in children with specific etiology cough can go a long way towards mitigating mortality and morbidity due to respiratory illnesses in children.

Keywords: Chronic cough; Children; Recurrent respiratory infections; Vitamin D supplementation

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Introduction

Acute Respiratory Infection (ARI) in the pediatric age group is rampant to the extent of qualifying as a public health problem worldwide [1]. Taking cognizance of the whopping figures of the mortality and DALYs (Disease Adjusted Life Years) lost to the same, the WHO (World Health Organization) adopted a goal of substantial reduction in the mortality and morbidity inherent to respiratory infections among children, as part of its Millennium Development Goal (numbered 4). The international community moved a step further to adopt/emancipate to the Sustainable Development Goals (SDGs) as a paradigm shift realizing further investment towards the effect of reducing childhood mortality attributable to respiratory infections [2].

Acute Respiratory Infections (ARI) are a major burden to child health in developing countries

like India [Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, *et al.,*] Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000 [3].

To quote scientifically, it is not formidable to predict the direct temporal relation between acute respiratory infections being harbringers to what we label as Recurrent Respiratory Infections (RRIs) and entities like Chronic Cough. This however is notwithstanding the fact that the aforementioned morbidities may well bear their origins from various developmental, congenital, cardiac and even gastrointestinal conditions that present as RRIs and chronic cough. In this context, it is imperative to mention that whereas there are potentially effective vaccines and antibiotics towards primary and secondary prevention of these two entities; yet a most deserving concept of primordial prevention has till date assumed a backseat for want of research and systematic reviews exploring the biological hypothesis (es) or a biological association with population micronutrient quanta (in deficiency or excess). To add to the plausibility, the roles of zinc and Vitamin A have been known to have been studied worldwide over decades and important deductions proposed to the extent of impacting 'evidence based practice'. However, despite knowledge and evidence of the role of Vitamin D in the implication of a cohort of medical morbidities among children, its role has not yet been explored and/or harnessed thereby in RRIs and chronic cough among paediatric population.

The present study thus aims at investigating the potential role of Vitamin D supplementation in children with RRIs and chronic cough and their subsequent respiratory performance.

Recurrent respiratory tract infections are one of the most frequent reasons for pediatric visits and hospitalization.

The primary objectives of the study are as under:

1. To evaluate serum Vitamin D levels in cases of Recurrent Respiratory Infections & Chronic Cough.

2. To investigate the effect of Vitamin D therapy on recurrence of disease/Chronic cough.

Methods

Methodological considerations

1. RRIs and Chronic cough being the exposure variables in the study are hypothesized to bear an association with Vitamin D deficiency. The outcome measure also includes improvement in symptoms in terms of severity and reduction in frequency of the above morbid episodes with appropriate supplementation of oral Vitamin D in candidate patients. Further to the same, it is obvious that certain confounders may play definitive role in discerning a true scientific causal association between the two. One of such confounders may be family diet, Hypovitaminosis due to genetic or renal defects, complementary and breast feeding practices, socio economic status of the family, sun exposure and chronic diseases attributed to non respiratory etiologies, and the like.

2. In order to mitigate of such potential confounders, we may and have attempted to use the stratification design for selected variables but the same have not been statistically evaluated in depth. The binary logistic regression technique is a promising measure to obviate the effect of confounding factors statistically, and the same has harnessed to precision in the current study to the extent of establishing an association between the various variables of exposure *vis a vis* one of the outcome measures, that is presence or absence of Vitamin D deficiency. However, ours being a prospective interventional study and not merely an observational study, this purpose can only be fulfilled in partial extent if we chose to harness the logistic regression technique. However, since the same is one of the secondary objectives of our study, the authors do still recommend the use of the aforesaid statistical technique in order to deduce certain serendipitous conclusions.

3. Conducting an RCT (Randomized Control Trial), which is considered gold standard in most of scientific medical research, was not feasible in our case of a hospital based setting, wherein children with RRIs and chronic cough would need to be allocated/randomized into two groups; one would receive Vitamin D supplementation and the other a placebo. In an ideal setting, this would not conform to being toughly sound; besides another hurdle based on the fact that the clinical investigator would know as to which group would receive the drug and which group is subject to placebo. This would not amount to be random and therefore be less valid scientifically.

4. A case can be made for employing the use of 'case control study' for the current study design but the same is a retrospective observational study and would have been suitable only in case we were to examine the Vitamin D status among children with chronic cough and RRIs. However, the main disadvantage of this technique would have been recall bias, and also that we have conducted a potential intervention in the form of micronutrient supplementation in question.

5. A prospective interventional study design was thus chosen to be most appropriate for this study.

Study design

Hospital based Prospective interventional study conducted at the Pulmonology and Infectious Disease Clinic, Department of Paediatrics in collaboration with the Rajiv Gandhi Endocrinology Centre, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh.

Study duration

Nov 2016 to June 2018.

Subjects

Children between the ages of 6 months to 14 years and presenting with Chronic Cough & Recurrent Respiratory Infections to the Paediatric Out Patient Department on Mondays and Thursdays of each week. A written consent for inclusion in the study was had from the parents/wards of the recruited children.

Sample size

All eligible patients reporting to the Outpatient, Pulmonology and Infectious Diseases Clinic during the study period full filling the inclusion criteria were included.

Sampling technique

A pilot study spanning a month was carried out towards this effect where in an estimation of the number of children presenting with Chronic Cough and RRIs qualifying under the operational definitions of the two conditions (mentioned as under) were included. The estimation results of the foretasted pilot study enrolled a total out of 1200 cases, of whom 10 patients had a diagnosis of Chronic Cough & 5 had Recurrent Respiratory Infections, contributing roughly to a proportion of 1.25%.

As the study was outpatient based and patients were enrolled only twice a week, an estimated sample size over the proposed study duration of 20 months was calculated as under: (15x20)/3=100 patients. Accounting for an additive/attrition effect 10%, a minimum sample of 110 patients was targeted for the study.

Inclusion criteria

Consecutive children presenting with Recurrent Respiratory Infections and Chronic Cough on specified Out Patient days (Consecutive sampling).

Exclusion criteria

(i) All children with congenital heart disease, hereditary immunodeficiency diseases, tumors, prior surgery, gastro-esophageal reflux disease and foreign body inhalation.

(ii) Patients whose parents refused to give their consent for their inclusion in the study.

Ethical issues

Consent-written informed consent was taken from parents and from children aged above 12 years. Approval for conducting the study was taken from institutional ethics committee JNMCH.

Study instruments

1. Pro forma-Detailed history and examination regarding presenting complaints and those relevant to Chronic Cough & Recurrent Respiratory Infection *viz*., mode of delivery, duration of breast feeding, exposure to sun, anthropometry and exploring for specific causes for chronic cough or RRIs etc were recorded in a pretested and validated pro forma.

All included children were subjected to estimation of Vitamin D, calcium, phosphate. Nasopharyngeal swab, bronchoalveolar lavage with microscopy and culture was done where indicated and permitted.

X ray chest was done. HRCT was done where patient(s) failed to respond to treatment for 4 weeks or as indicated a priori.

Intervention

On the basis of level of Vitamin D levels, children were classified into 'deficient', 'insufficient' and 'sufficient' with their levels in ranges of <15 ng/ml, 15-20 ng/ml and >20 ng/ml respectively. Venous blood sample was drawn & sent to endocrinology lab & central lab on the same day or stored at -20ºC if sample transfer was not feasible the same day.

Children with serum Vitamin D levels <15 ng/ml were administered Vitamin D3 (cholecalciferol) 5000 IU/day for 3 months. Vitamin D3 therapy of 400 IU/day was administered to patients with serum levels in the range of 15-20 ng/ml.

Specific Treatment was administered wherever the cause of chronic cough was identified. In cases where no cause could be identified but nasopharyngeal aspirates/sputum showed neutrophils/ macrophages and detectable microorganism on body fluid/tissue cultures, a 2 weeks course of oral amoxycillin and clavulanic acid was given considering the same to be Protracted Bacterial Bronchitis (PBB), wherever applicable. Rest of the children was advised symptomatic treatment in the form of steam inhalation anti histamines, and/or bronchodilators.

Outcome measures

For the first 4 weeks patients, were observed for relief of symptoms in terms of time taken for disappearance of symptoms (Response).

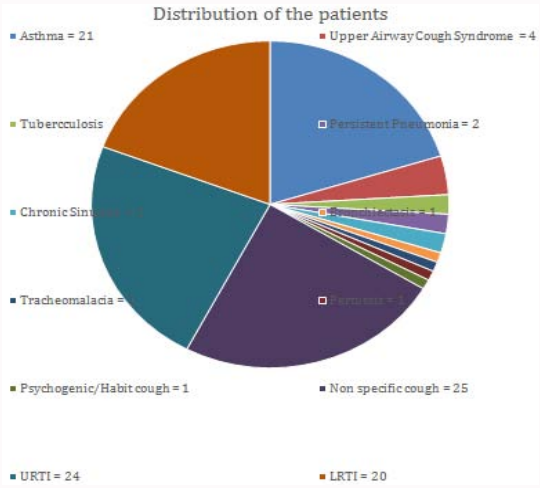

Figure 1: Proportionate distribution of study patients with respect to type/ etiology of cough.

Follow up

Patients were followed every three months subsequently for recurrences up to duration of 12 months.

Operational definitions

(1) Chronic cough: Cough lasting for more than four weeks was described as chronic cough.

(2) Chronic cough with known cause/Specific Chronic cough: Chronic cough having specific cause *i.e.,* Bronchial Asthma, Upper Airways Cough Syndrome, Pertusis etc.

(3) Chronic cough with unknown cause/Non specific cough: Chronic Cough in which cause could not identified.

(4) RRI: A child with URTI at least 6 times or LRTI at least 2 times per year was defined as RRI.

(5) URTI: Diagnosis of Rhinitis, Nasopharyngitis, Oropharyngitis, and Tonsillitis, Laryngitis or Otitis media was evaluated as URTI.

(6) LRTI: Tracheitis, Bronchitis, Bronchiolitis and pneumonia were assessed as LRTI.

(7) Remission/Response to treatment: Complete disappearance of symptoms for at least one week.

(8) Recurrence: Reappearance of symptoms and persisting for at least one week.

(9) Family history of atopy: Patients whom first or second degree relative (siblings, parent and grandparents) had asthma, atopic dermatitis or allergic rhinitis.

Statistical analysis

The SPSS 22 software for windows was used for statistical analysis. Continuous variables were expressed as mean, standard deviation and range. Independent t-test was used to compare means of a variable for 2 groups and chi square test and ANOVA for multiple variables. A '*P*' value <0.05 was considered statistically significant.

Results

Figure 1 depicts the various etiologies of chronic cough and RRIs

Table 1: Age wise distribution of Vitamin D status at the onset of study.

	Deficient		Insufficient		Sufficient	
Age	N=31		N=39		N=34	
Group	Chronic cough	RRI	Chronic cough	RRI	Chronic cough	RRI
6 months to 1 year N=36	5 (27.8)	7(53.8)	8 (33.3)	7(46.7)	5(27.8)	4(25.0)
1 year to 5 year N=32	7(38.9)	4(30.8)	4 (16.7)	5(33.3)	6(33.3)	6(37.5)
5 year to 14 years N=36	6(33.3)	2(15.4)	12(50.0)	3(20.0)	7(38.9)	6(37.5)
Total N=104	18(100.0)	13(100.0)	24(100.0)	15(100.0)	18(100.0)	16(100.0)

Chi square=1.219, df=5, *p*=0.65, Not significant

Table 2: Nutritional status of the study population.

	Deficient	Insufficient
Wasting	6	10
Stunting	4	15
Both	5	7

Chi square= 1.787, df=2, *P*=0.40, Not significant

Table 3: Nutritional status with respect to blood Vitamin D levels.

	Chronic cough	RRI	Total
Normal/mild	20	22	43
Moderate malnutrition	36	19	55
Severe malnutrition	4	2	5
Obese	0	1	1

Chi square=5.953, df=6, *P*=0.428, Not significant

Table 4: Number of patients in group A, B and C before and after treatment.

	Number of patients N=35	
	Before Treatment N (%)	After treatment N (%)
Deficient	10 (28.6)	1(0+0+1)-(2.9)
Insufficient	14 (40.0)	5 (1+3+1)-(14.3)
Sufficient	11(31.4)	29(9+11+9)-(82.8)

Table 5: Number of patients having recurrence of cough during follow up after Vitamin D supplementation.

	Deficient	Insufficient	Sufficient
	N=10	N=15	N=12
Recurrent	4	5	5
Non recurrent	6	8	7

in the study population. Non specific cough, URTI, Asthma and Pulmonary Tuberculosis were the chief diagnoses in that order.

As shown in Table 1, there was no significant difference between the number of patients in different groups of Vitamin D levels (Deficient, Insufficient, and Sufficient).

Of the 15 and 32 children found to be Vitamin D deficient and insufficient respectively, 46% of those in the insufficient category were stunted *vis a vis* 26% in the deficient group. Wasting however was more prevalent in the Vitamin D deficient group (40%) versus 31% in the insufficient group. However, this difference was not found to be statistically significant ($p>0.05$) (Table 2).

When categorized into different grades of malnutrition by z scores (WHO), a majority of children were moderately malnourished. However the nutritional status as per z scores did not bear a statistically significant association ($p>0$, 05) the cough entities studied (Table 3).

Specific chronic cough

Most of the patients (83%) belonging to deficient and insufficient

Table 6: Status of Vitamin D before and after treatment.

Vitamin D status	Before supplementation	After supplementation
Deficient	9 (36.0)	4 (3+0+1)-16
Insufficient	10 (40.0)	7 (2+2+3)-28
Sufficient	6 (24.0)	14 (4+8+2)-56

Table 7: Number of patients having recurrence during follow up.

	Deficient	Insufficient	Sufficient
	N=10	N=10	N=7
Recurrent	3	3	3
Non recurrent	5	7	4

*Drop out =2

Table 8 (A): Stepwise binary logistic regression analysis for multivariate analysis of selected variables in chronic cough and Vitamin D status.

Variable	EC	SE of E	OR	P
Gender	-2.55	28.7	0.91	0.84
SE class	12.41	27.3	0.63	0.68
Diet	-7.59	1.8	4.89	0.04
Wasting	2.88	0.55	0.66	0.04
Stunting	-6.59	1.8	5.72	0.04
Specific cough	7.02	19.41	0.96	0.54
Non respiratory causes	-8.88	1.2	4.44	0.03

Table 8 (B): Stepwise binary logistic regression analysis for multivariate analysis of selected variables in Recurrent RRIs and Vitamin D status.

Variable	EC	SE of E	OR	P
Gender	0.306	0.333	1.358	0.359
SE class	0.639	0.448	1.895	0.153
Diet	0.719	0.507	1.911	0.192
Wasting	0.92	0.335	2.508	0.006
Stunting	-0.247	0.12	0.781	0.04
Specific cough	0.937	0.617	1.922	0.213
Non respiratory causes	0.812	0.577	1.522	0.31

category became Vitamin D sufficient after treatment. However, in one chronic cough patient the Vitamin D levels declined from sufficient to the deficient levels at 3 months (Table 4).

As many as 40% of initially deficient children showed recurrences, 38% of initially insufficient children showed recurrences and while 42% of sufficient children showed recurrences (Table 5).

Non specific chronic cough

Most of the patients (63%) belonging to deficient and insufficient category became Vitamin D sufficient after treatment. However, the levels of 50% of patients belonging to sufficient group declined to

Table 9: Status of Vitamin D before and after treatment.

Vitamin D Status	Before Treatment (%)	After Treatment (%)
Deficient	5 (25.0)	2 (0+0+2)-10
Insufficient	10(50.0)	5 (3+2+0)-25
Sufficient	5(25.0)	13(2+8+3)-65

Table 10: Number of patients having recurrence during follow up.

	Deficient	Insufficient	Sufficient
	N=5	N=10	N=7
Recurrent	2	3	2
Non recurrent	3	5	5

*Drop out = 2

insufficiency and 17% declined to deficiency levels (Table 6).

As many as 37.5% of initially deficient children showed recurrences, 30% of initially insufficient children showed recurrences and while 4% of sufficient children showed recurrences (Table 7).

On stepwise binary logistic regression with reference to chronic cough and Vitamin D status, Dietary practices, wasting, stunting and non respiratory causes emerged as significant predictors obviating the influence of potential confounder (Table 8A).

On stepwise binary logistic regression with reference to RRIs and Vitamin D status, only wasting and stunting emerged as significant predictors obviating the influence of potential confounders (Table 8B).

Most of the patients (67%) belonging to deficient and insufficient category became Vitamin D sufficient after treatment. However, in two patients the Vitamin D levels declined from sufficient to the deficiency levels at 3 months (Table 9).

40% of initially deficient children showed recurrences, 38% of initially insufficient children showed recurrences and while 29% of sufficient children showed recurrences (Table 10).

Discussion

In our prospective randomized control study, we found that while the mean presenting age was 61.9 (+8.3 months); infants dominated the RRI group and school age children largely formed the chronic cough group (Table 1). The difference can be attributed to the fact that cases of fast breathing and cough are operationally categorized into varying grades of pneumonia for ease of recognition, immediate management and referral by the peripheral health workers in developing countries. A significant proportion of these patients testify to diagnoses as bronchial asthma, GERD and even Congenital Heart Disease only later in their natural history of disease. The clearer manifestations of asthma beyond infancy may be the reason for dominance of school age group in chronic cough cases, as found by Razi *et al.,* [4].

The gender difference was also not found to be significant in our study (M:F 53:51) (Table 2), quite in consonance with allied studies. In our study, 44% children were underweight and no statistically significant difference was observed between incidences of chronic cough and RRI in the follow up period (Table 3). Not many studies have analysed this association though.

Of remark nonetheless was the statistically significant difference ($p<0.05$) in RRI s and chronic cough in exclusively breastfed *vis a vis* those not so (as per UNICEF and WHO guidelines) [5], all the more emphasizing the protective role of breastfeeding. Ozdemer *et al.,* also studied the correlation between duration/appropriateness of breastfeeding with RRIs and chronic cough but did not report any statistically significant difference. In the very same study, the mean levels of 25(OH) D in RRI and Chronic cough cases were lower so than what were estimated in ours. The same could be attributed to the fact that their recruits were children living in temperate climates in contrast to our candidate children from the tropics.

The mean duration of non specific cough was significantly protracted in as compared to etiologies qualifying for specific cough diagnoses in all the three groups in our study. More so, the Vitamin D deficient group had longer duration of symptoms, followed suit by those among insufficient and sufficient groups (Table 10). The difference was statistically significant in specific cough case since treatment is largely symptomatic and empirical in non specific cough cases for want of an etiology. A majority of specific cough cases comprised of Bronchial asthma, and the same bears a known association with Vitamin D deficiency. This adds to our proposition that the duration of symptom duration is significantly prolonged among these children when compared with those in sufficient group.

In two studies from Canada, Vitamin D status was not associated with hospitalization risk for ALRI [6].

However, the difference was that the Bell's population curve of Vitamin D distribution in the Canadian study population was not in structural consonance with that of Indian children. The levels in their study were found to be substantially higher. The probable reason was that most of the Canadian infants and toddlers were consuming either Vitamin D fortified infant formula or milk, or received Vitamin D supplements if exclusively breast-fed. Therefore, there may be important cofactors like host nutritional status and infectious aetiology apart from a Vitamin D threshold below which ALRI risk begins to increase above baseline.

Besides, a study from India by Wyse V *et al.,* 2004 [7] concluded that subclinical Vitamin D deficiency was a significant risk factor for severe acute lower respiratory tract infection (ALRI) in Indian children of pertinent remark was the observation of a statistically significant improvement in Vitamin D levels among group A and B children following appropriate/recommended supplementation. However, it is interesting to note that a child from group C (highlighted in green) actually remained deficient despite supplementation. In a similar vein, whereas a majority of the patients (60%) with upper respiratory tract infections from among the deficient and insufficient categories became Vitamin D sufficient after treatment. two patients exhibited decline in Vitamin D levels upon 3 months of follow up.

A multitude of chronic infections and associated squeal that accompany and scourge the holistic health of young children in developing countries like ours, other systemic disorders and consequent allied macro and micronutrient deficiencies may well be responsible for such a skewed effect.

Interestingly, one study by Roth DE *et al.,* [8] suggested reverse causality for this observation that is ALRI suppressing 25(OH) levels, although other confounding factors could be present (factors which cause or predispose to respiratory infections also causing Vitamin D deficiency).

As many as 40% of initially deficient children, 38% of insufficient children and 42% of sufficient children showed recurrences

respectively on follow up. Because most of the children had significant improvement in their Vitamin D status, it is proposed that their immunity had improved with supplementation thus asserting to our observation that no statistically significant difference existed as far as recurrence was concerned.

Also, two recent studies of importance has highlighted that notwithstanding the fact that Vitamin D has a pivotal role in enhancing childhood immunity in general, yet children with normal Vitamin D levels but low Immunoglobulin assays tend to suffer from prolonged, more severe and protracted respiratory morbidities [9]. Worthwhile to mention therefore is that Vitamin D levels may not be the sole determinant towards childhood respiratory morbidity and mortality in the long term. Serum immunoglobulin levels too have been shown to be a potential stakeholder towards this effect, and the same calls for further studies.

Notwithstanding though, the maintenance of sufficient Vitamin D level homeostasis cannot be undermined towards emancipation of respiratory health of children and toddlers. A prudent message herein to be disseminated is that covariates and allied morbid determinants play confounders towards ultimate interpretation of the hypothesis of Vitamin D supplementation in children with varying cough states and their recurrence [10]. This tantamounts to a limitation as well, yet reiterating the beneficial effects of Vitamin D supplementation in recurrent RRIs and non specific and specific cough from the major findings of our study.

The study of relation between the respiratory illnesses and Vitamin D status is also confounded by other factors like breastfeeding and the geographical location in which the patient is residing.

Conclusion

Vitamin D adequacy has a pertinent role towards prevention of recurrent RRIs and chronic specific/non specific coughs of different etiologies. Apart from administering specific and supportive treatment, a case can be made to probe in specifically for clinical/subclinical Hypovitaminosis D in such candidate children. Feeding practices, immune status and concurrent nutritional and infectious illnesses have to be addressed in tandem while managing children with RRIs and chronic cough. Vitamin D supplementation alone, even in children with insufficiency will not be fully contributory to their ultimate respiratory health unless aforementioned concurrent issues are dealt with. Also, designing future studies to do so would be an important step in the development of functional pediatric definitions of 'Vitamin D deficiency' to attain uniformity and enable comparisons especially among different geographical locations. With increasing rate of Vitamin D deficiency and ease of supplementation in case of deficiency, Vitamin D supplementation is likely to become a highly effective intervention in reducing child morbidity and progressing a step ahead towards fulfillment of the much desirable Millennium Development Goals 2020. Community screening and surveys for detection and management of wasting and study can be harnessed towards long term strategy and possible policy formulation towards this effect in concordance with a strong political will.

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