Vitamin A-fortified monosodium glutamate and vitamin A status: a controlled field trial[1-4]

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ABSTRACT A controlled trial of fortification of crystalline monosodium glutamate (MSG) with 810 μg RE vitamin A/g was undertaken in an area of endemic vitamin A deficiency in Indonesia. Powdered MSG was used to mask the yellow color of the vitamin A. Fortified MSG was marketed through ordinary channels in five villages in the program area and five nearby villages served as the control area. The product retained 84% of its potency after 4 mo and 57% after 11 mo in the marketplace. Base-line serum and breast-milk vitamin A levels were slightly higher in the control areas. Follow-up serum levels increased dramatically in program villages, 0.67 ± 0.33 at prefortification base line to 0.92 ± 0.33 μmol/L ($p < 0.001$) at 11 mo after introduction of the fortified product. Breast-milk levels also rose, from 0.60 ± 0.29 at base line to 0.67 ± 0.30 μmol/L at 11 mo ($p < 0.05$). Serum and breast-milk levels in control villages did not change. *Am J Clin Nutr* 1988;48:1265–70.

KEY WORDS Monosodium glutamate (MSG), vitamin A, fortification, xerophthalmia

Introduction

Vitamin A deficiency has long been a major nutritional problem in Indonesia. A national xerophthalmia survey completed in 1980 (1, 2) revealed that the mean prevalence of Bitot's spots among preschool children in the rural area as a whole was ~1% while that of active corneal disease related to vitamin A deficiency was 6.4/10 000, both well above WHO criteria for a public health problem (3). It was estimated that 50 000 children were in danger of becoming blind every year. In addition, subsequent studies indicate that Indonesian children with vitamin A deficiency are at increased risk of respiratory disease, diarrhea, and mortality. (4, 5) Mass dosing with vitamin A capsules reduced childhood mortality by 35–70%. (6, 7)

To control the problem three intervention strategies have been considered: nutrition education, supplementation through distribution of a large dose of vitamin A (60 000 μg RE [200 000 IU]) twice a year, and fortification of a commonly consumed item with vitamin A. Dietary modification through nutrition education is underway but is considered a long-term, slowly accepted solution. Biannual distribution of high doses of vitamin A has been carried out through various delivery systems for > 15 y. However it has proven too costly to expand beyond the highest risk areas and coverage has fallen from an initial high of ≥ 80% to 40–50%.

A nationwide program of fortifying sugar in Guatemala (8) and a pilot study of MSG fortification in the Philippines (9) demonstrated the potential feasibility and impact of this approach. Financial and technical problems, however, interfered with expansion and/or continuation of these activities.

The Government of Indonesia has decided that fortification of a commonly consumed dietary item with vitamin A could prove an effective means of controlling most vitamin A deficiency. A national survey (1, 2) revealed that four substances, white sugar, flour, MSG, and salt, reached the high-risk target groups. Of these four potential vehicles, MSG most closely fulfilled the necessary conditions for fortification: production was highly centralized; MSG reached the largest proportion of target

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children and mothers with relatively little variation in per capita consumption; and the poorest, highest-risk segments of society purchased MSG in small packets whereas wealthier families purchased large packages, permitting fortification to be targeted to small packets thus reducing vitamin A wastage.

MSG is metabolized quickly in the body (10). It is generally recognized as a safe additive (11), WHO considering the maximal permissable daily intake to be 150 mg/kg body wt (12). Maximum recorded daily intakes for children in Indonesia rarely exceed 85 $mg \cdot kg^{-1} \cdot d^{-1}$ (Muhilal, unpublished observation).

This paper reports a pilot MSG-fortification project in Indonesia that utilized a novel method for overcoming technical and organoleptic obstacles to the fortification process and that had a demonstrable and significant impact on serum vitamin A levels of children and breast-milk levels of lactating mothers residing in program villages.

Methods

The level of vitamin A added to MSG was determined from the amount needed to supplement dietary sources to prevent serious deficiency in relation to the quantity of MSG consumed by the target high-risk group. The average amount of MSG consumed by preschool children was calculated from in-depth dietary assessments of rural families by considering the proportion of all family foods prepared with MSG that were consumed by the children. This amounted to an average of 0.23 ± 0.20 g MSG/d. We estimated that the addition of 50% of the preschool Recommended Dietary Allowance (~450 μg RE; Muhilal, T Apunain, D Karyadi, et al, unpublished observations, 1983) would provide children with an adequate total daily intake of vitamin A. Thus, the amount of the vitamin added to MSG was 210 μg RE/0.23 g (~810 μg RE vitamin A/g MSG).

The vitamin A used in this study was type 250-CWS (75 000 μg RE/g, cold-water storage) supplied by Hoffman-La Roche, Basle. To mask the yellow color of the vitamin A, which has negative connotations in Indonesia where MSG is promoted as being a pure white substance, vitamin A was covered with finely ground MSG dust. We first mixed 800 g of vitamin A 250-CWS with 60 g of hydroxypropyl cellulose that had been dissolved in 450 mL ethyl alcohol to serve as the binding agent or glue. This mixture was then combined with 3200 g of 100-mesh MSG powder so that MSG powder stuck to the vitamin A particles. This premix was then dried by fanning and mixed using a Patterson-Kelly blender (East Stroudsburg, PA) with commercial MSG crystals at a 5:95 ratio until it was homogeneous. This MSG-A contained ~810 μg RE of vitamin A/g.

The study was carried out in a rural, traditional rice-eating area in West Java ~20 km from the city of Bogor. Of the three major MSG producers in Indonesia, one (PT Sasa Inti, Surabaya, Indonesia), controlled the highest proportion (80%) of the market in the study area and was willing to cooperate with the project. The Sasa brand was, therefore, selected for fortification. Packets of MSG marketed in the study area varied in size from 0.65 to 13.6 g. All these sizes were included in the fortification scheme. The MSG-A was marketed through normal channels and without promotion. It was produced in the Sasa factory in Surabaya, ~965 km away, then sent to the agent at the nearest city (Bogor) to the program area. From this agent the MSG-A was sold to markets and foodstalls in five villages in the study area; in the control area, composed of five nearby villages, nonfortified MSG was marketed as usual.

The five villages in the program area consisted of 48 subvillages; those in control areas consisted of 44 subvillages. The research team did not participate in the marketing. At regular intervals packets of MSG and MSG-A were purchased from all village foodstalls and vitamin A content was assayed. The samples were obtained at 1, 2, 4, 6, 9, and 11 mo after marketing began. Samples were also obtained at the consumer level from 10 households in each village. The quantitative analysis of vitamin A in MSG was performed by the spectrophotometric method (13). A quick test for vitamin A content of MSG-A in the field was performed semiquantitatively by a modification of the Carr-Price reaction (14) as follows: ~15 g MSG was mixed with ~0.5 mL trichloroacetic acid in chloroform; the blue color that appeared in several seconds was compared with standard blue colors equivalent to 150, 300, 450, 600, and 900 μg RE. This quick test was used for screening whether or not quantitative analysis was necessary and in monitoring the penetration of MSG-A into the two study areas.

Program and control areas contained ~5500 preschool-age children (0–5 y) each. Children were examined three times: at base line and at 5 and 11 mo after MSG-A was introduced (6 and 12 mo after base line). Ages were ascertained directly from parents with the aid of a local events calendar. Field workers visited every household 2 d before the examination to obtain informed consent from the mothers and to ask that they bring their preschool children to a central site where the children would undergo medical, anthropometric, and ophthalmologic examinations. These findings are reported elsewhere (15). Approximately 70% of the mothers brought their children to the examination site at each of the rounds. Samples of blood for vitamin A analysis were collected from an independent, systematic sample of at least 200 program and control children at each round by using a random start and selecting every 16th subject to arrive at the central site. Therefore, children whose blood was obtained at base line were rarely the same children who contributed blood at the subsequent visit. Follow-up blood samples could not be collected on the same children because mothers objected to collection of more than one blood sample. The sample of children donating specimens at each round was taken to be representative of all children examined at that particular round. Samples of breast milk were taken from mothers who, at the time of examination, were still breast-feeding their babies < 6 mo of age. Breast-milk samples of ≥ 25 mL were collected in the middle of a feed between 0900 and 1200 by use of a manual pump. Samples were kept at −20 °C until analysis.

Blood samples were collected from finger tips in four to five capillary tubes. The tubes were sealed with molten candle wax and then placed in an ice thermos. When the samples reached the laboratory several hours later, the serum was separated and kept at −20 °C until analysis.

Vitamin A levels in the serum were determined by HPLC (13). Breast-milk samples were analyzed by the trifluouroacetic acid method (16). Before analysis, breast-milk samples were incubated with an equal volume of 1 mol KOH/L in 95% alcohol for 30 min at 60 °C because preliminary analysis indicated optimal results were obtained with this preparation.

Trained nutritionists assessed 24-h dietary intake on two consecutive days from a 4% random subsample of families. An abbreviated method was employed that focused particularly on

TABLE 1
Retention of vitamin A in MSG-A in relation to the duration at market

Length of time marketed	Number of samples	Vitamin A level	Percent retention
mo	*n*	*μg RE/g**	%
0	10	810 ± 390	100.0
1	42	795 ± 395	98.1
2	42	750 ± 308	92.6
4	42	675 ± 418	83.3
6	42	555 ± 418	68.5
9	42	480 ± 355	59.3
11	42	465 ± 318	57.4

* ±SD.

food sources of β-carotene (leafy greens, yellow fruits and fibers, etc). The purpose was to provide estimates of base-line comparability between program and control groups.

Statistical analysis utilized Students *t* test for the difference between means and chi-square for the shift in distributions (17). The primary objective of analysis was the change in each group over time. Midyear and 12-mo measurements were compared with those at base line in the same group to reveal whether the effect of fortification on program children was progressive. Control villages adjacent and similar to the program area were followed in the same fashion to identify changes in vitamin A status that might have been unrelated to fortification (eg, seasonality, annual variation in harvests, etc).

Results

MSG-A marketing commenced in January 1985, 1 mo after base-line data were collected. MSG-A penetrated three control subvillages. The reverse also occurred: six subvillages in the program area did not receive MSG-A because they were closer to markets and foodstalls in the control area. The data from these nine cross-contaminated subvillages were excluded before any comparisons, leaving 5755 children in the program area and 5445 in the control area.

Retention of vitamin A in MSG-A in relation to duration at market is shown in **Table 1**.

There were no significant differences in dietary consumption by preschool program and control children at base-line examination (**Table 2**). As expected, consumption of β-carotene was low, representing only 30% of the RDA for vitamin A (Muhilal, T Apunain, D Karyadi, et al, unpublished observations, 1983) despite the emphasis placed on assessing the intake of this nutrient. Other reported nutrient intakes are low due in part to the shortened design of the dietary questionnaire.

TABLE 2
Daily nutrient consumption of program and control children*

Energy and nutrient	Program group (n = 138)	Control group (n = 137)
Energy (kcal)	496 ± 287	518 ± 309
Protein (g)	13 ± 9	14 ± 9
Fat (g)	12 ± 9	13 ± 9
Carotene (μg)	718 ± 1047	789 ± 1203
Vitamin C (mg)	18 ± 21	22 ± 29
Iron (mg)	3.2 ± 2.7	3.6 ± 3.3

* $\bar{x}$ ± SD.

TABLE 3
Mean serum vitamin A before and after MSG-A marketing

Group	Duration of marketing MSG-A	Number of samples	Serum vitamin A*
	mo	*n*	*μmol/L*
Program	0	205	0.67 ± 0.33
	5	258	0.78 ± 0.32†
	11	217	0.92 ± 0.33†
Control	0	240	0.78 ± 0.35
	5	289	0.71 ± 0.30‡
	11	290	0.72 ± 0.33‡

* $\bar{x}$ ± SD.
† $p < 0.001$ (increase) compared with level at 0 mo in program area.
‡ $p < 0.05$ (decrease) compared to 0 mo in control area.

Base-line serum vitamin A levels were lower in the program villages (**Table 3**). Levels in program villages rose significantly between base line and the 5-mo follow-up and rose still higher by 11 mo. Serum vitamin A levels in the control group fell significantly below base line at 5 and 11 mo.

There was a significant shift in serum vitamin A levels over time in program-village children but not in control-village children (**Table 4, Fig 1**). The improved distribution of serum vitamin A levels among program children was statistically significant ($p < 0.05$).

Vitamin A levels in breast milk of lactating mothers in program and control areas were similar at base line (**Table 5, Fig 2**). Five months after the marketing of MSG-A, the vitamin A in breast milk in the program area rose significantly. Eleven months after the marketing of MSG-A the vitamin A in the breast milk remained at this higher level. In the control group, breast-milk vitamin A levels at 5 and 11 mo were below those at base line.

Discussion

Just as in many developing countries, vitamin A deficiency is prevalent in Indonesia (1, 2). From previous work (2) and from base-line values in this study, almost half the preschool children have serum vitamin A levels < 0.70 μmol/L.

A nationwide survey revealed that most xerophthalmic children have regular access to β-carotene–rich dark green leafy vegetables (2, 18). Unfortunately these are consumed in small amounts if at all. Nutrition-education campaigns have had little success in raising consumption in Indonesia and more aggressive, comprehensive strategies are planned for the future.

To date, the major approach to combatting vitamin A

TABLE 4
Distribution of serum vitamin A values before and after MSG-A marketing

Group	Duration of marketing MSG-A	Total number of children	Serum vitamin A		
			<0.35 μmol/L	0.35–0.69 μmol/L	≥0.70 μmol/L
	mo	*n*	*n* [%]	*n* [%]	*n* [%]
Program	0	205	21 [10.2]	78 [38.0]	106 [51.8]
	5	258	10 [3.9]	93 [36.0]	155 [60.1]
	11	217	8 [3.7]	56 [25.8]	153 [70.5]
Control	0	240	22 [9.2]	93 [38.8]	125 [52.0]
	5	289	29 [10.0]	121 [41.9]	139 [48.1]
	11	290	30 [10.3]	115 [39.7]	145 [50.0]

deficiency in Indonesia has been periodic distribution, every 6 mo, of UNICEF-supplied capsules of 60 000 μg RE vitamin A to preschool children in high-risk areas either through a special, dedicated system or integrated into established multipurpose programs. Various pilot studies demonstrated the effectiveness of this approach for reducing xerophthalmia and blindness rates (19, 20) and mortality (6). Unfortunately coverage rates fall with time to ~40–50% of the target group (19); those missed are usually in greatest need (7). The cost of distribution can prove prohibitive (19).

Fortification of a commonly consumed dietary item provides a potential mechanism for overcoming many of these limitations. The main problem lies in identifying a suitable vehicle: one that is consumed in substantial amounts by a large proportion of the children with significant vitamin A deficiency; that passes through a small number of central processing plants where fortification can be readily accomplished and supervised; and for which there is relatively little variation in consumption among potential recipients, permitting levels of fortification that ensure adequate amounts of vitamin A to reach the target children without overdosing maximum consumers. In Indonesia MSG, a popular food enhancer, best met these criteria.

Concerns about acceptability were allayed by the marketing and distribution figures from the manufacturer during the intervention period, which indicated that MSG sales were unchanged after fortification. Further, daily MSG consumption levels were the same in the program and control villages for both adults (0.40 and 0.41 g/d, respectively) and preschool children (0.24 and 0.21 g/d, respectively), supporting our earlier, small-scale

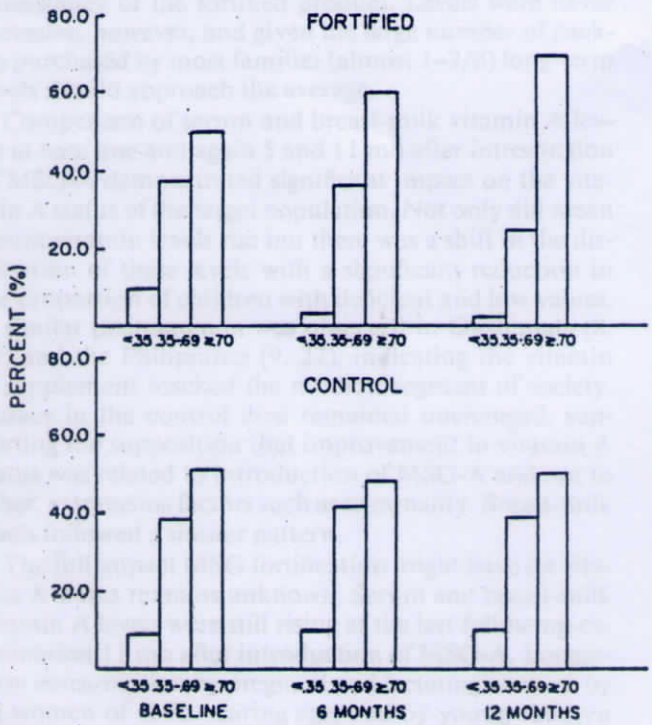

FIG 1. Distribution of serum vitamin A levels among children from program (upper graph) and control (lower graph) villages at base line and at 5 and 11 mo after introduction of fortified MSG in the program area (6 and 12 mo after base line).

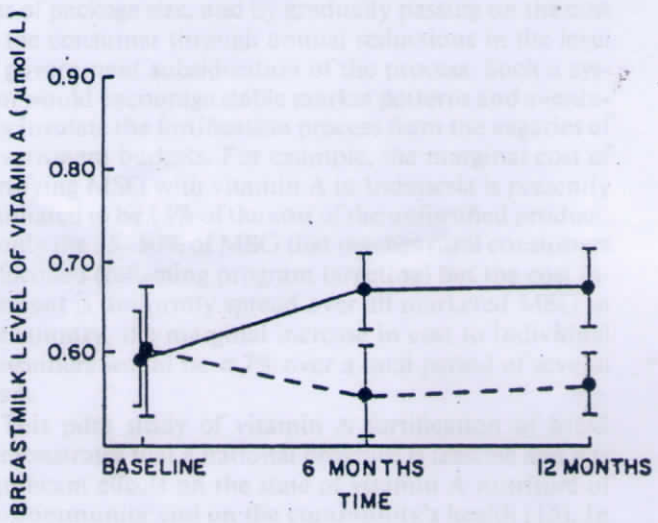

FIG 2. Mean levels and 95% confidence limits of vitamin A in the breast milk of lactating mothers at base line and at 5 and 11 mo after introduction of fortified MSG in the program area (solid line) and continued use of nonfortified MSG in the control area (broken line).

TABLE 5
Vitamin A level in breast milk among lactating mothers before and after MSG-A marketing

Duration of marketing MSG-A	Program area		Control area	
	Number of samples	Breast-milk vitamin A level*	Number of samples	Breast-milk vitamin A level*
mo	*n*	*μmol/L*	*n*	*μmol/L*
0	178	0.60 ± 0.29	200	0.61 ± 0.45
5	218	0.67 ± 0.27†	245	0.58 ± 0.35
11	263	0.67 ± 0.30†	192	0.58 ± 0.20

* $\bar{x} \pm$ SD.
† Increase in value compared with 0 mo $p < 0.05$.

studies on the organoleptic acceptability of the fortified product.

Our approach also overcame one of the technical difficulties encountered in a pilot Philippines trial (R Florentino, personal communication, 1980), where fine powder migrated between the walls of the containers preventing water-tight heat sealing. As a result early samples in the Philippines suffered rapid loss of potency. In contrast our assay of samples purchased from local markets retained > 50% of vitamin A at 11 mo. Although even this level is far from ideal, marketing surveys indicate that most MSG reaches consumers within 2–4 mo after leaving the factory, when retention rates are well in excess of 80%. The large standard deviation of mean vitamin A content at base line indicates some problems with consistancy of the fortified product. Levels were never excessive, however, and given the large number of packets purchased by most families (almost 1–2/d) long-term levels should approach the average.

Comparison of serum and breast-milk vitamin A levels at base line and again 5 and 11 mo after introduction of MSG-A demonstrated significant impact on the vitamin A status of the target population. Not only did mean serum vitamin levels rise but there was a shift in the distribution of these levels with a significant reduction in the proportion of children with deficient and low values. A similar phenomenon was observed in Guatemala (8, 21) and the Philippines (9, 22), indicating the vitamin A supplement reached the neediest segment of society. Values in the control area remained unchanged, supporting the supposition that improvement in vitamin A status was related to introduction of MSG-A and not to other, extraneous factors such as seasonality. Breast-milk levels followed a similar pattern.

The full impact MSG fortification might have on vitamin A status remains unknown. Serum and breast-milk vitamin A levels were still rising at the last follow-up examination 11 mo after introduction of MSG-A. Longer-term consumption by pregnant and lactating women, by all women of child-bearing age, and by young children might raise vitamin A levels further and move a larger group of children (including infants) into a state of adequate vitamin A reserves. The impact should also be greater if all MSG marketed to this population is fortified not just the 80% controlled by one manufacturer.

Unlike the early Philippine trials the MSG-A was not promoted or provided free of charge. The cost of fortification was subsidized to retain parity in price between the fortified and nonfortified product. MSG consumption rates remained unchanged. The manner in which the added cost of fortification is handled is critical especially because the Indonesian government has adopted a policy of nationwide fortification. In the Philippines (9, 23) the cost of fortification was covered by reducing the MSG content of the fortified packets. This led consumers to purchase larger packets of nonfortified MSG that provided them with more MSG for their money. In Guatemala sugar manufacturers were responsible for absorbing the cost of fortification. With a fall in world sugar prices and rise in the cost of vitamin A however, they were forced to suspend fortification.

The government of Indonesia will probably circumvent these potential problems by requiring that all MSG in packages below a certain size be fortified, that the cost of fortification be spread over all MSG produced regardless of package size, and by gradually passing on the cost to the consumer through annual reductions in the level of government subsidization of the process. Such a system would encourage stable market patterns and eventually insulate the fortification process from the vagaries of government budgets. For example, the marginal cost of fortifying MSG with vitamin A in Indonesia is presently estimated to be 13% of the cost of the unfortified product. If only the 35–50% of MSG that reaches rural consumers is fortified (reflecting program targeting) but the cost increment is uniformly spread over all marketed MSG in the country, the marginal increase in cost to individual consumers would be < 7% over a total period of several years.

This pilot study of vitamin A fortification of MSG demonstrates that a national program is feasible and has significant effects on the state of vitamin A nutriture of the community and on the community's health (15). In the next phase towards national fortification, the program will be expanded to a far larger area. In the interim, MSG producers will need time to develop the capacity

to produce and deliver the fortified product on a large scale.

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