Randomised, double blind, placebo controlled clinical trial of efficacy of vitamin A treatment in non-measles childhood pneumonia

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Abstract

Objective: To evaluate the impact on clinical recovery and severity of the addition of large doses of vitamin A to the standard treatment for childhood pneumonia.

Design: A randomised, double blind, placebo controlled trial.

Setting: Study children were recruited at a public hospital in Recife, north east Brazil, an area of marginal vitamin A deficiency.

Subjects: 472 children aged 6 to 59 months with clinical diagnosis of pneumonia.

Interventions: 200 000 IU (infants) or 400 000 IU (1-4 year olds) of vitamin A in oil or similar capsules of placebo divided into two daily oral doses, in addition to the standard treatment.

Main outcome measures: Duration of the episode and incidence of adverse outcomes.

Results: The groups were similar with respect to overall duration of pneumonia and incidence of adverse outcomes. Children who received vitamin A, however, were less likely to have fever by day 3 ($P=0.008$) and were 29% less likely to fail to respond to the first line antibiotic ($P=0.054$).

Conclusion: There was little evidence for an effect of vitamin A treatment on the immediate outcome of the pneumonia episode.

Introduction

Acute respiratory infections are the leading cause of mortality and morbidity in children less than 5 years of age in developing countries. They are associated with or cause about 3.8 million childhood deaths annually; 30.3% of all deaths in this age group.¹ Pneumonia is responsible for most of these deaths.

Despite an impressive effect on reducing overall child mortality,²⁻⁴ prophylactic vitamin A supplementation has not been shown to reduce either incidence of or mortality from pneumonia.⁵ When used therapeutically in doses of at least 400 000 IU for children or 200 000 IU for infants with measles, however, many cases of which are complicated by pneumonia, vitamin A has been shown to reduce case fatality,⁶⁻⁸ severity of illness,⁷⁻⁹ and duration of pneumonia.⁷⁻⁸ In contrast, in two trials which used a smaller treatment dose of vita-

min A for measles (corresponding to 200 000 IU of vitamin A for 1-4 year old patients) no significant impact was observed on the incidence of or recovery from pneumonia or on case fatality,¹⁰⁻¹¹ although one of these studies reported an effect on duration and severity of diarrhoea and on the incidence of otitis media.¹⁰

The exact mechanism by which vitamin A exerts its effect on reduction of mortality has not been established, but it may be mediated at least in part by enhanced regeneration of the epithelium and an improved systemic immune response to infection.¹² The results of previous studies suggest that the impact of vitamin A supplementation on morbidity and mortality from pneumonia may vary according to dose, prophylactic or therapeutic use, and the nature, severity, and aetiology of the disease.

We therefore set out to examine whether cases of pneumonia not related to measles could also benefit from the administration of large doses of vitamin A. The main aims of this study were to evaluate the impact on clinical recovery and the incidence of adverse effects of the addition of large doses of vitamin A to the standard treatment for childhood pneumonia and to relate any impact to the aetiology and severity of pneumonia.

Patients and methods

A randomised, double blind, placebo controlled clinical trial was carried out at the Barão de Lucena Hospital, one of the main general public hospitals in Recife, north east Brazil. A total of 472 children aged 6 to 59 months with a clinical diagnosis of pneumonia, either admitted to hospital ($n=259$) or treated as outpatients ($n=213$), were recruited to the trial between June 1994 and June 1995 and received either vitamin A or identical looking capsules of placebo (Tishcon, United States) in addition to the standard pneumonia treatment. The study was approved by the ethics committees of the London School of Hygiene and Tropical Medicine and the Barao de Lucena Hospital.

The study paediatricians made the diagnosis of pneumonia after taking a detailed history and examining the children for signs of lung infection—such as fever, tachypnoea, signs of dyspnoea, and consolidation. Although a positive radiological image was not

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required for the confirmation of the diagnosis, chest x ray pictures were used to aid the clinical diagnosis. The following exclusion criteria were applied: xerophthalmia, previous admission to hospital associated with the current illness, renal failure, measles, other major concurrent infection (for example, septicaemia, meningitis), other active lung disease, and parental refusal. Residents outside Recife metropolitan area who were treated as outpatients were also excluded. No cases of xerophthalmia, renal failure, or measles were seen. Xerophthalmia is rare in the study area, but subclinical vitamin A deficiency is common; serum retinol concentrations below 0.7 $\mu\text{mol/l}$ have previously been found in 34.1% of children aged 2 to 5 years.¹³

Children were individually randomised into one of the two treatment groups. The randomisation was blocked into groups of four and the randomisation scheme separately applied for inpatients and outpatients and infants and 1-4 year olds. The vitamin A or placebo capsules were put into small brown envelopes labelled with identification numbers. The vitamin A capsules contained 100 000 IU of vitamin A and 20 IU of vitamin E in oil. Infants were given one capsule on admission to the trial and another the next day. The 1-4 year olds received two capsules on each of these occasions. Children who had received vitamin A supplements in the preceding month ($n = 27$) received capsules only on admission.

When children were admitted to the trial baseline data were collected on demographic, biological, and socioeconomic characteristics and a baseline clinical evaluation was carried out. This included a chest x ray picture taken in the posteroanterior position, the analysis of venous blood for serum retinol concentra-

tions analysed by high pressure liquid chromatography,¹⁴ and routine haematological tests, as well as an aetiological investigation. This included blood cultures and culture of pleural fluid when available and antigen detection for *Haemophilus influenzae* group B and *Streptococcus pneumoniae* by latex agglutination from urine samples (Wellcogen, Murex Diagnostics, United Kingdom) after concentration of the urine with a disposable concentrator (Minicon B-15 concentrator, Amicon, United States). Antigens for respiratory syncytial virus, influenza virus A and B, parainfluenza types 1, 2, and 3, adenovirus and *Chlamydia* species were detected by direct immunofluorescence from nasopharyngeal swab samples, by using commercial monoclonal antibodies conjugated with fluorescein isothiocyanate (IMAGEN, Dako, Denmark). Serology for *Mycoplasma pneumoniae* antibody detection was performed by an indirect agglutination test (Serodia-Myco II, Fujirebio, Japan). The aetiological diagnosis was established whenever any of the tests yielded a positive result.

All children were evaluated by the study paediatricians on admission to the trial and on the 3rd and 11th days. In addition, daily clinical evaluations were made up to day 11 or longer for children who remained in hospital beyond this point. This daily evaluation focused on the observation of signs and symptoms of disease and severity and the occurrence of adverse outcomes and was conducted by a paediatrician while children were in hospital. Children who were at home were visited by a trained field worker who completed a simplified evaluation form. Twenty six patients (14 in the vitamin A group and 12 in the placebo group) who lived outside the Recife metropolitan area and who

Fig 1 Recovery from pneumonia, admission to hospital, and signs of disease in children given vitamin A or placebo

were discharged from hospital after less than 10 days were not followed up at home. Apart from these, and a small number of missed visits, there were no losses to follow up.

All evaluations were performed by study team members once a day, except for temperature which was taken four times daily for inpatients. Fever was defined as any axillary temperature measurement $\geq 37.8^{\circ}\text{C}$. Two measurements of respiratory rate were taken over one minute with World Health Organisation acute respiratory infection respiration timers. Tachypnoea was defined if both measurements were ≥ 50 per minute in infants or 40 per minute in those aged from 12 months. Oxygen saturation was measured with Ohmeda Biox 3740 pulse oximeters (Ohmeda, United States). Desaturation was defined as values lower than 92%. For the purpose of data analysis, the episode of pneumonia was considered to be resolved on the first day that the child was free from fever, tachypnoea, and any sign of dyspnoea, including lower chest indrawing, nasal flaring, cyanosis, grunting and hypoxaemia, and accepting food and liquids. Admission to and discharge from hospital were decided by the hospital paediatricians in accordance with the children's clinical condition.

Quality assurance and control included standardisation of study procedures, production of detailed manuals describing the study procedures, a four week pilot study, intensive staff training, and regular staff meetings. Data were entered twice by two independent computer assistants soon after collection and compared daily. Daily manual and regular computerised data monitoring was carried out to check completeness and consistency of data as well as reliability between observers. A subsample of all evaluations and laboratory tests was repeated blind. Care was taken to guarantee the adequate collection, storage, and transport of laboratory samples (for example, appropriate temperature and protection from light and air when appropriate). Fourteen vitamin A or placebo capsules were analysed blind, confirming the adequacy of randomisation and dosage.

The sample size chosen for the study was adequate to detect, with a power of 90% at the 5% significance level, a reduction of one day in the mean duration of pneumonia from 8 days to 7 days and a 12.5% reduction in the proportion of patients with any adverse effect, assuming one would occur in 25% of controls.

Data were entered in dBase IV (Ashton-Tate, USA) and analysed with SPSS-PC 5.0 (SPSS, Chicago), EPI-INFO 6.0 (Centers for Disease Control, Atlanta), and STATA 4.0 (Stata, Texas). All data analysis was carried out according to a pre-established analysis plan. Proportions were compared by using χ^2 tests with continuity correction or Fisher's exact test when appropriate.¹⁵ Multivariate analyses were conducted with logistic regression.¹⁶ The durations of episodes and signs of disease were compared by using proportional hazards regression.¹⁷ Mean serum retinol concentrations were compared by *t* test¹⁵ and analysis of covariance.¹⁸ Comparisons were made both with and without adjustment for prognostic covariates. Except for when major differences occurred the results are all those of unadjusted analyses. Two sided significance tests were used throughout.

Results

The treatment groups were broadly similar at baseline (table 1). Mean serum retinol concentrations on day 11 were $1.04\text{ }\mu\text{mol/l}$ in the vitamin A group and $0.91\text{ }\mu\text{mol/l}$ in the placebo group ($P = 0.009$). The difference in the values between the groups when the baseline serum retinol concentrations were taken into account, however, was not significant at 5% (mean difference $0.11\text{ }\mu\text{mol/l}$; $P = 0.078$).

Figure 1 shows similar patterns of recovery in the two treatment groups for pneumonia episode, admission to hospital, and individual signs of pneumonia (fever and tachypnoea). The median duration of the episode was 7.6 days in the vitamin A group and 7.5 days in the placebo group. The groups also showed similar prevalences of signs of pneumonia two days after recruitment (day 3), used as an indication of early recovery, except for fever which was lower in the vitamin A group (16% *v* 26.4% in the placebo group; $P = 0.008$).

The groups also experienced similar risks of complication (table 2). Children who received placebo, however, failed to respond satisfactorily to the first line antibiotic more often (rate ratio = 0.71; 95% confidence interval 0.50 to 1.01; $P = 0.054$). Among children in hospital, when the timing of the antibiotic change was also taken into account, the association with treat-

Table 1 Baseline comparability of selected variables between treatment groups. Figures are numbers (percentages) of children unless stated otherwise

Detail	Vitamin A (n=239)	Placebo (n=233)
Boys	141 (59)	116 (50)
Median age (months)	18	19
Mean (SD) birth weight (g)	3120 (633)	3122 (533)
Median duration of breast feeding (months)	2.9	3.2
Median family size	5	5
Pneumonia in previous 12 months	62 (26)	58 (25)
Admission to hospital in previous 12 months	83 (35)	77 (33)
Current admission with radiologically confirmed pneumonia	200 (84)	206 (89)
Aetiology:		
Bacteria	61 (28)	56 (26)
Virus	19 (9)	18 (8)
<i>Chlamydia</i> or <i>Mycoplasma</i>	2 (1)	1 (1)
Mixed	7 (3)	5 (2)
Not identified	132 (60)	137 (63)
Mean (SD) serum retinol ($\mu\text{mol/l}$)†	0.45 (0.34)	0.38 (0.28)
Serum retinol $<0.7\text{ }\mu\text{mol/l}$ †	137 (82)	140 (86)
Tachypnoea	128 (54)	128 (55)
Temperature $\geq 37.8^{\circ}\text{C}$	80 (34)	92 (40)
Indrawing of chest	121 (51)	117 (50)
Oxygen saturation $\leq 92\text{ mm Hg}$	80 (34)	92 (39)
Lung complications	27 (11)	29 (12)
Extrapulmonary complications	41 (17)	38 (16)
Diarrhoea	33 (14)	33 (14)
Diet:		
Normal	59 (25)	68 (29)
Diminished	155 (65)	132 (57)
Refused food	25 (11)	33 (14)
Mean (SD) weight for height z score	-0.76 (1.23)	-0.72 (1.15)

*Samples collected were adequate for all tests in 438 (92.8 %) patients: 221 in vitamin A group and 217 in placebo group.

††In subsample of 329 (70%): 167 in vitamin A group and 162 in placebo group.

Table 2 Incidence of adverse outcomes and change in antibiotics according to treatment

Outcome	No (%) taking vitamin A (n=239)	No (%) taking placebo (n=233)	Rate ratio (95% CI)
Death	2 (1)	2 (1)	0.97 (0.14 to 6.86)
Lung complications	5 (2)	3 (1)	1.62 (0.39 to 6.72)
Other complications	17 (7)	22 (9)	0.75 (0.41 to 1.38)
Hospital admission*	10 (9)	4 (4)	2.39 (0.77 to 7.37)
Antibiotic change	43 (18)	59 (25)	0.71 (0.50 to 1.01)
Any of the above	61 (26)	75 (32)	0.79 (0.60 to 1.06)

*Outpatients only: 109 in vitamin A group and 104 in placebo group.

Table 3 Incidence of potential side effects* according to treatment

Side effect	No (%) taking vitamin A	No (%) taking placebo	Rate ratio (95% CI)
Vomiting	27/171 (16)	34/167 (20)	0.78 (0.49 to 1.23)
Diarrhoea	19/206 (9)	30/199 (15)	0.61 (0.36 to 1.05)
Irritability	38/157 (24)	38/149 (26)	0.95 (0.64 to 1.40)
Bulging fontanelle	4/99 (4)	0/87	—
Any of the above	84/239 (35)	94/233 (40)	0.87 (0.67 to 1.10)

*Between 24 and 72 hours after start of treatment.

ment became more marked (hazards ratio = 0.56; 95% confidence interval 0.35 to 0.92; $P=0.02$). Thus, children on placebo not only needed the antibiotic treatment changed more often, but, when this was the case, they also needed it earlier in the course of the episode.

Bulging fontanelle was observed in 4/99 (4%) of the children in the vitamin A group whose fontanelle had not closed. This disappeared in less than 48 hours in all cases. None of the children who received placebo (0/87) developed this complication ($P=0.12$). The groups showed similar incidences of irritability, vomiting, and diarrhoea (table 3).

We found no evidence of any interaction between treatment and whether the aetiological agent was viral or bacterial with respect to recovery from pneumonia (table 4). Although there was a suggestion of a trend towards a better response for both these aetiological groups compared with those children from whom no pathogen was identified, indicated by the higher recovery rate ratios, this was not significant. We also found a slight trend towards a better response among patients admitted to hospital compared with those treated as outpatients, with some suggestion of an interaction with respect to recovery from the episode

($P=0.10$), fever ($P=0.06$), and tachypnoea ($P=0.04$) but not with respect to the incidence of adverse outcomes ($P=0.21$) (table 4).

Discussion

There have been three vitamin A treatment trials, in Guatemala,¹⁹ the United States,²⁰ and Tanzania,²¹ which have looked at acute lower respiratory infections not related to measles, but none has focused specifically on pneumonia. They all failed to show an impact on either recovery from or the severity of the infection. The vitamin A dose used in the Guatemalan study (100 000 IU to 200 000 IU), however, did not lead to an improvement in serum retinol concentrations, which suggests that the dose might have been insufficient to demonstrate any potential beneficial impact. Moreover, vitamin A deficiency was not prevalent in this population, as indicated by the high median baseline serum retinol concentrations around 0.90 $\mu\text{mol/l}$ even in the presence of an acute infection. Likewise, children infected with respiratory syncytial virus in the North American study had normal vitamin A concentrations and the total dose used was relatively small (100 000 IU for all treated children). In addition, the conclusions of this study are compromised by the very small sample size of only 32 children. In the study in Tanzania, as in our study, higher doses of vitamin A were used (200 000 IU to 400 000 IU) in a population likely to be vitamin A deficient but still with no evidence of benefit from vitamin A administration.

We looked at the impact of vitamin A treatment of childhood pneumonia. The doses of vitamin A were comparable with those used in the most effective measles trials, as were the baseline retinol concentrations. The low serum retinol baseline values were probably because of the acute infection process,²² as indicated by the marked increase by day 11 in the placebo group. Serum retinol concentrations were higher on day 11 in the vitamin A group, however, suggesting both that the treatment was effective and that there was some underlying deficiency in this population. We did not measure serum retinol in the first days after vitamin A administration, but their peak concentrations might have been associated with the lower prevalence of fever on day 3 and the lower rate of change in antibiotics. The daily monitoring of data does not suggest major safety concerns. The transitory bulging fontanelle, detected in 4% of the vitamin A treated patients, has been shown in other situations where large doses of vitamin A were

Table 4 Recovery from pneumonia and incidence of adverse outcomes according to aetiology and severity of disease

Detail	No (%) of children	Recovery rate ratio (95% CI)*			Risk ratio (95% CI)† for any adverse outcome
		Episode	Fever	Tachypnoea	
Aetiology‡:					
Bacterial	110 (26)	1.20 (0.76 to 1.91)	1.41 (0.92 to 2.17)	1.32 (0.84 to 2.09)	0.63 (0.34 to 1.15)
Viral	36 (9)	1.10 (0.49 to 2.50)	1.10 (0.45 to 2.66)	0.99 (0.41 to 2.38)	0.45 (0.13 to 1.54)
Not detected	277 (66)	0.88 (0.66 to 1.18)	1.02 (0.76 to 1.37)	0.94 (0.70 to 1.28)	0.92 (0.64 to 1.32)
Interaction test		P=0.16	P=0.40	P=0.19	P=0.28
Type of treatment:					
Outpatient	213 (45)	0.76 (0.55 to 1.04)	0.84 (0.61 to 1.18)	0.75 (0.54 to 1.05)	0.99 (0.61 to 1.62)
Admitted to hospital	259 (55)	1.09 (0.80 to 1.49)	1.27 (0.94 to 1.72)	1.22 (0.88 to 1.68)	0.70 (0.49 to 0.99)
Interaction test		P=0.10	P=0.06	P=0.04	P=0.21

*Hazards rate for recovery in vitamin A compared with placebo group. Values > 1 are in favour of vitamin A group.

†Risk rate in vitamin A compared with placebo group. Values > 1 are in favour of placebo group.

‡Excluding 34 children with incomplete tests, 12 with mixed infections, two cases of chlamydia infection, and one case of mycoplasma infection.

used²³⁻²⁶ and is thought unlikely to have long term consequences.²⁵

Overall, the results of our study show a lack of impact of vitamin A on the progression of pneumonia, suggesting that the response to vitamin A is probably specific to pneumonia associated with measles, and thus the benefits of its administration cannot be generalised to other pneumonias. As previously suggested the form of vitamin A preparation used should also be considered.¹¹⁻¹⁹ The two measles trials which gave the most impressive results in favour of vitamin A used water miscible preparations,⁷⁻⁹ in contrast with this and other studies on acute lower respiratory infections⁶⁻¹⁰⁻¹¹⁻¹⁹⁻²¹ in which an oil based preparation, as recommended by the WHO, was used.

Effect of aetiological agent

We found no evidence that cases of pneumonia due to specific aetiological groups (bacterial or viral) respond to vitamin A. Despite the small number of confirmed viral cases, we also looked at the results separately for cases due to the paramyxoviruses (respiratory syncytial virus and parainfluenza) from the same family as the measles virus but found that, similar to the group of viruses in general, they seemed to show no impact of vitamin A. We acknowledge that our study lacks power to examine effectiveness of treatment according to specific aetiological agents, however, and that therefore no definitive conclusions can be made. Most cases with a positive aetiological diagnosis in our study were bacterial. Even if the vitamin A were to have an effect in these cases this might be masked by the use of an effective treatment such as antibiotics. Interestingly, we found that children treated with vitamin A responded better to the first line antibiotic used and thus were less likely than children from the placebo group to require second line antibiotics. Whether this represents a consistent effect of vitamin A or is the result of chance would need confirmation from further studies. If such is the case then a true, even if small, association between vitamin A and recovery from pneumonia could have been obscured by the efficient use of second line antibiotics if needed.

Another interesting finding was the evidence of some interaction between treatment with vitamin A and severity of disease on presentation, with results slightly in favour of the vitamin A group among patients initially admitted to hospital, the opposite occurring among those treated as outpatients. Although this finding comes from a subgroup analysis which was preplanned, in no case did the different response between the treatment groups reach significance at the 5% level. Supplementation trials, however, have suggested the impact of vitamin A to be on disease severity,² and even the convincing results of vitamin A treatment on measles⁶⁻¹⁰ were not confirmed in the only trial where outpatients, supposedly less severely affected, were studied.¹¹

Conclusions

The findings of this study do not provide evidence in favour of a general benefit of vitamin A in the treatment of pneumonia. Although a subgroup of patients, perhaps the most severely affected or most vitamin A deficient, could attain some benefit from vitamin A treatment, any conclusion in such a direction

Key messages

- Pneumonia is a leading cause of childhood mortality in developing countries
- Vitamin A supplementation has no impact on mortality from pneumonia even though it reduces overall mortality
- Treatment of measles pneumonia with vitamin A reduces case fatality and severity of disease
- This study showed that vitamin A treatment has no impact on the recovery from non-measles pneumonia, despite some suggestion that severely affected patients may benefit
- The addition of vitamin A for treatment protocols for childhood pneumonia is not recommended for clinical cure, although it maybe a useful contact to improve vitamin A status

would depend on future stronger evidence. Thus, we conclude that the findings of this study are consistent with the lack of impact of prophylactic vitamin A supplementation on incidence of and mortality from pneumonia⁵ and with other studies of vitamin A treatment of acute lower respiratory infection.¹⁹⁻²¹

At present we do not consider that the addition of vitamin A to the treatment protocols for childhood pneumonia in areas like Recife, where vitamin A deficiency is marginal, should be recommended solely on the basis of any potential improvement in recovery from the acute episode of pneumonia. Improving vitamin A status in populations where the deficiency is an important public health problem is justified by its impact on mortality and the severity of other illnesses, particularly measles and diarrhoea.² Contacts with the health services because of diseases such as pneumonia may constitute a good opportunity for supplementation. Serum retinol concentrations are not accurate indicators of total body reserves²²⁻²⁷ but the slightly greater improvement in retinol concentrations at the end of the episode in supplemented children provided some evidence that vitamin A stores may have been improved in these patients. The results on the impact on morbidity over four months after the pneumonia episode, which was also evaluated in a further stage of this study, will provide additional information on the appropriateness of supplementing children when they are acutely ill with pneumonia.

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- 1 Kirkwood BR, Gove S, Rogers S, Lob-Levyt J, Arthur P, Campbell H. Potential interventions for the prevention of childhood pneumonia in developing countries: a systematic review. *Bull WHO* 1995;73:793-8.
- 2 Beaton GH, Martorell R, L'Abbé KA, Edmonston B, McCabe G, Ross AC, et al. *Effectiveness of vitamin A supplementation in the control of young child*

- morbidity and mortality in developing countries. Toronto: University of Toronto, 1992.
- 3 Glasziou PP, Mackerras DEM. Vitamin A supplementation in infectious diseases: a meta-analysis. *BMJ* 1993;306:366-70.
 - 4 Fawzi WW, Chalmers TC, Herrera MG, Mosteller F. Vitamin A supplementation and child mortality, a meta-analysis. *JAMA* 1993;269:899-903.
 - 5 The Vitamin A and Pneumonia Working Group. Potential interventions for the prevention of childhood pneumonia in developing countries: a meta-analysis of data from field trials to assess the impact of vitamin A supplementation on pneumonia morbidity and mortality. *Bull WHO* 1995;73:609-19.
 - 6 Barclay AJG, Foster A, Sommer A. Vitamin A supplements and mortality related to measles: a randomised clinical trial. *BMJ* 1987;294:294-6.
 - 7 Hussey GD, Klein M. A randomized controlled trial of vitamin A in children with severe measles. *N Engl J Med* 1990;323:160-4.
 - 8 Madhulika, Kabra SK, Talati A. Vitamin A supplementation in post-measles complications. *J Trop Pediatr* 1994;40:305-7.
 - 9 Coutosoudis A, Broughton M, Coovadia HM. Vitamin A supplementation reduces measles morbidity in young African children: a randomised, placebo-controlled, double-blind trial. *Am J Clin Nutr* 1991;54:890-5.
 - 10 Ogaro FO, Orinda VA, Onyango FE, Black RE. Effect of vitamin A on diarrhoeal and respiratory complications of measles. *Trop Geogr Med* 1993;45:283-6.
 - 11 Rosales FJ, Kjolhede C, Goodman S. Efficacy of a single oral dose of 200,000 IU of oil-soluble Vitamin A in measles-associated morbidity. *Am J Epidemiol* 1996;143:413-22.
 - 12 Sommer A, West KP Jr. *Vitamin A deficiency, health, survival, and vision*. New York: Oxford University Press, 1996.
 - 13 McAuliffe J, Santos LMP, Diniz AS, Batista Filho M, Barbosa RCC. A deficiência de vitamina A e estratégias para seu controle: Um guia para as Secretarias Municipais de Saúde. Fortaleza, Brazil: Projeto Hope, 1991.
 - 14 De Ruyter MGM, De Leenheer AP. Determination of serum retinol (vitamin A) by high-speed liquid chromatography. *Clin Chem* 1976;22:1593.
 - 15 Kirkwood BR. *Essentials of medical statistics*. Oxford: Blackwell Scientific Publications, 1988.
 - 16 Hosmer DW, Lemeshow S. *Applied logistic regression analysis*. New York: Wiley, 1989.
 - 17 Cox DR, Oakes D. *Analysis of survival data*. London: Chapman and Hall, 1984.
 - 18 Armitage P, Berry G. *Statistical methods in medical research*. 2nd ed. Oxford: Blackwell Scientific Publications, 1987.
 - 19 Kjolhede CL, Chew FJ, Gadomski AM, Marroquin DP. Clinical trial of vitamin A as adjuvant treatment for lower respiratory tract infections. *J Pediatr* 1995;126:807-12.
 - 20 Kyran P, Quinlan KP, Hayani KC. Vitamin A and respiratory syncytial virus infection. *Arch Pediatr Adolesc Med* 1996;150:25-30.
 - 21 Fawzi WW, Mbise RL, Fataki M, Herrera MG, Kawau F, Ndossi G, et al. Effect of vitamin A supplements in reducing severity of lower respiratory infections among children in Tanzania. Presented to the meeting of the International Vitamin A Consultative Group in Guatemala in March 1996. Guatemala: IVACG, 1996 (Abstracts XVII).
 - 22 Coutosoudis A, Coovadia M, Broughton M, Salisbury RT, Elson I. Micronutrient utilisation during measles treated with vitamin A or placebo. *Int J Vitam Nutr Res* 1991;61:199-204.
 - 23 West KP, Khatri SK, LeClerq SC, Adhikari R, See L, Kat J, et al. Tolerance of young infants to a single, large dose of vitamin A: a randomised community trial in Nepal. *Bull WHO* 1992;70:733-9.
 - 24 de Francisco A, Chakraborty J, Chowdhury HR, Yunus M, Baqui AH, Diddique AK, et al. Acute toxicity of vitamin A given with vaccines in infancy. *Lancet* 1993;342:526-7.
 - 25 Agoestina T, Humphrey JH, Taylor GA, Usman A, Subardja D, Hidayat S, et al. Safety of one 52- μ mol/l (50 000 IU) oral dose of vitamin A administered to neonates. *Bull WHO* 1994;6:859-68.
 - 26 Rahman MM, Mahalanabis D, Wahed MA, Aminul Islam M, Habte D. Administration of 25 000 IU vitamin A doses at routine immunisation in young infants. *Eur J Clin Nutr* 1995;49:439-45.
 - 27 Olson JA. Serum retinol levels of vitamin A and carotenoids as reflectors of nutritional status. *J Natl Cancer Inst* 1984;73:1439-44.

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Acute upper gastrointestinal haemorrhage in west of Scotland: case ascertainment study

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Abstract

Objectives: To determine the incidence and case fatality of acute upper gastrointestinal haemorrhage in the west of Scotland and to identify associated factors.

Design: Case ascertainment study.

Setting: All hospitals treating adults with acute upper gastrointestinal haemorrhage in the west of Scotland.

Subjects: 1882 patients aged 15 years and over treated in hospitals for acute upper gastrointestinal haemorrhage during a six month period.

Main outcome measures: Incidence of acute upper gastrointestinal haemorrhage per 100 000 population per year, and case fatality.

Results: The annual incidence was 172 per 100 000 people aged 15 and over. The annual population mortality was 14.0 per 100 000. Both were higher among elderly people, men, and patients resident in areas of greater social deprivation. Overall case fatality was 8.2%. This was higher among those who bled as inpatients after admission for other reasons (42%) and those admitted as tertiary referrals (16%). Factors associated with increased case fatality were age, uraemia, pre-existing malignancy, hepatic failure, hypotension, cardiac failure, and frank haematemesis or a history of syncope at presentation. Social deprivation, sex, and anaemia were not associated with increased case fatality after adjustment for other factors.

Conclusions: The incidence of acute upper gastrointestinal haemorrhage was 67% greater than the highest previously reported incidence in the United Kingdom, which may be partially attributable to the greater social deprivation in the west of Scotland and may be related to the increased prevalence of *Helicobacter pylori*. Fatality after acute upper gastrointestinal haemorrhage was associated with age, comorbidity, hypotension, and raised blood urea concentrations on admission. Although deprivation was associated with increased incidence, it was not related to the risk of fatality.

Introduction

Acute upper gastrointestinal haemorrhage is a common reason for admission to hospitals in the United Kingdom. Until recently, knowledge of the epidemiology of this problem was based on small series with inadequate data on the denominator of the population. These series have reported case fatality (the proportion of cases dying) rather than population based mortality, which better reflects need. A recent large multicentre population based study of acute upper gastrointestinal haemorrhage in four English health regions found an incidence twice as high as expected.¹ However, this was lower than the incidence reported in north east Scotland,² which then had the highest reported incidence in the United Kingdom.