# Accuracy of clinical assessment of deep-vein thrombosis

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## Summary

The clinical diagnosis of deep-vein thrombosis is generally thought to be unreliable. From experience, we hypothesised that this widely held view might be incorrect. We developed a clinical model and prospectively tested its ability in three tertiary care centres to stratify symptomatic outpatients with suspected deep-vein thrombosis into groups with high, moderate, or low probability groups of deep-vein thrombosis. We evaluated our clinical model in combination with venous ultrasonography to determine the potential for an improved and simplified diagnostic approach in patients with suspected deep-vein thrombosis.

All patients were clinically assessed to determine the probability for deep-vein thrombosis before they had ultrasonography and venography. All tests were performed and interpreted by independent observers. In 529 patients, the clinical model predicted prevalence of deep-vein thrombosis in the three categories: 85% in the high pretest probability category, 33% in the moderate, and 5% in the low category. There was no statistical difference in the performance of the model in the three centres. The model demonstrated excellent interobserver reliability (Kappa=0·85). There were important differences with ultrasonography between the high and low pretest probability groups for both positive predictive values (100% (95% CI, 94–100%) *vs* (63% [35–85%], respectively).

Thus, use of the clinical model combined with ultrasonography would decrease the number of false positive and negative diagnosis if venography were done when the ultrasound result and pretest probability were discordant. The diagnostic process could be simplified by excluding those patients with low pretest probability and normal ultrasound results from serial testing.

*Lancet* 1995; **345:** 1326–30

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## Introduction

The diagnosis of deep-vein thrombosis (DVT) relies heavily on the use of objective tests because the symptoms and signs are not thought to be specific.[1,2] Venography is the reference standard for the diagnosis of DVT, but it is invasive, can be painful, is associated with allergic and other side effects, and it is not available in all centres.[3] Noninvasive tests such as venous ultrasonography and impedance plethysmography can replace venography in patients with clinically suspected DVT,[4] but are limited by the requirement for serial testing if the initial test is normal and by falsely abnormal results in 6% (ultrasonography) to 17% (impedance plethysmography) of patients.[5] Furthermore, most symptomatic patients do not have venous thrombosis and so serial testing is often unnecessary.

It has been our impression that clinical features can be used to classify many symptomatic patients with suspected DVT as having a high or low probability for DVT before diagnostic testing (ie, pretest probability). In support of this view, we reported[6] that a high proportion of patients who were strongly suspected of having DVT on clinical grounds, but who had normal impedance plethysmography, had demonstrable DVT by venography. Since the noninvasive diagnostic tests are not 100% accurate, the post-test probability of DVT is dependent on disease prevalence. Therefore, if it were possible to categorise the patient's pretest probability for DVT into low, moderate, or high, the diagnostic process would be improved by combining clinical diagnosis with noninvasive testing. For example, if the pretest probability of DVT is low and the noninvasive test result normal, the post-test probability of DVT may be low enough to obviate the need for serial testing. On the other hand, when there is discordance between the pre-test clinical probability and the noninvasive test result, the diagnosis may need to be confirmed or excluded by venography. We prospectively assessed the accuracy of a clinical model to determine the potential for improving and simplifying the diagnostic process when combined with venous ultrasonography in patients with suspected DVT.

## Methods

### *Patients and study design*

Our study involved three centres: the Henderson General Hospital and McMaster University Medical Centre in Hamilton, Ontario, Canada, and the Istituto di Semeiotica Medica, Padua, Italy. The study was approved by the institutional ethical review boards, and was done over 20 months at the Henderson Hospital (from March, 1992 to October, 1993) and 3 months at McMaster University Medical Centre (from July, 1993 to October, 1993). Outpatients referred for the evaluation of suspected DVT, who had symptoms for less than 60 days, were potentially eligible and were assessed by one of the physicians who regularly assess patients with thromboembolic disorders. Patients who met one or more of the following criteria were excluded: previous, objectively diagnosed DVT or pulmonary embolism; contraindication to contrast media (allergy or renal insufficiency); concomitant clinically suspected pulmonary

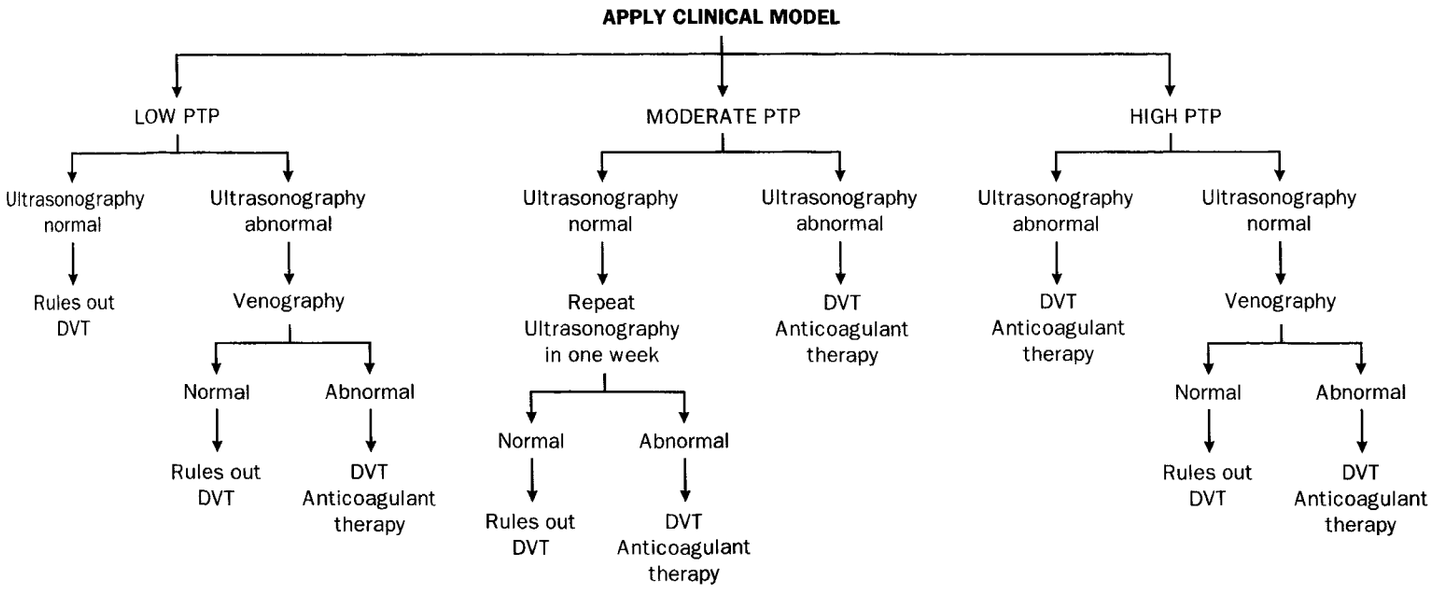


Figure: **Suggested diagnostic approach in outpatients with suspected DVT**

embolism; pregnancy; treatment with anticoagulant therapy for more than 48 h; below-knee amputation; or refusal to give informed consent. Patients with an obvious alternative cause for their symptoms and who had clinical features that were not compatible with DVT were excluded and did not have diagnostic testing. To confirm our results we did a prospective 6 month follow-up of this latter group of patients to determine whether they developed symptoms compatible with venous thromboembolism.

### *Clinical model*

We developed a clinical model before our study to stratify pretest probability for DVT into high, moderate, and low categories (table 1). Items included in the clinical model were assembled from information obtained by a literature review and from the collective experience of the participating investigators. These items fell into three groups: signs and symptoms of DVT, risk factors for DVT, and potential alternative diagnosis. The items were tabulated by the examining physician and a probability score was derived which categorised the patients into low, moderate, or high probability groups. The clinical model was tested in a pilot study of 100 outpatients with suspected DVT who had venography. Certain combinations of clinical factors were identified as being less predictive of DVT. The final clinical model was composed of specific items, designated as either major or minor, that included proven risk factors, and pertinent symptoms and physical signs at patient presentation. In patients with symptoms in both legs, the findings in the more symptomatic leg were used.

### *Diagnostic techniques*

Venography was done in all centres and additional ultrasonography was done in Padua and at the Henderson Hospital. Venography was usually performed on the same day as ultrasonography, but on the rare occasions when this was not possible, venography was done the next day. Ultrasonography and venography results were interpreted by a panel of at least three observers who were unaware of the other diagnostic test results and the patient's clinical history. In the case of disagreement the final result was determined by majority decision.

Ultrasonography, using real-time B-mode with compression only, was done with an ATL Ultramark 4 Plus (Advanced Technologies Laboratories, Bothell, WA, USA) and a 7·5 MHz and/or a 5·0 MHz transducer. We examined two areas of the leg: the common femoral vein at the inguinal ligament and the popliteal vein at the knee-joint line traced down to the point of the trifurcation of the calf-veins. No attempt was made to assess the deep veins at lower end of the calf. Veins were scanned in the transverse plane only. Lack of full compressibility was the sole criteria for an abnormal result; a vein was considered fully compressible if no residual lumen was seen.

Contrast venography was done with a modification of the techique of Rabinov and Paulin.[8] The sole criterion used for the diagnosis of acute DVT was a constant intraluminal filling defect in at least two projections. A venogram was normal if both peroneal and posterior tibial veins and the popliteal, superficial femoral, common femoral, and iliac veins were well opacified. All other test results were classified as inadequate. Thrombi were classified as proximal if they involved the popliteal or more proximal veins, or distal if they were isolated to the calf veins. Proximal thrombi were further categorised into those involving only the distal half of the popliteal vein, more than half the popliteal vein, and/or the other proximal veins. A thrombus was nonocclusive if contrast material was seen between the thrombus and the vessel wall along the entire course of the thrombus.

### *Analysis*

The sensitivity, specificity, and post-test probabilities of DVT with normal and abnormal ultrasound results (negative and positive predictive values, respectively) were calculated in each of the pretest probability categories. The comparison of the prevalence of DVT in each of the three pre-test probabilities, and the comparison of the performance of the clinical model in the three centres was done by a $2\times3$ $\chi^2$ analysis.[9] All p-values were based on two-tailed tests of significance. 95% CI were determined according to the binomial distribution.

The interobserver reliability of the model was determined in 34 patients by obtaining same-day assessments by two independent observers. Agreement was determined by a weighted Kappa test.[10]

## Results

### *Patient population*

887 consecutive, symptomatic outpatients were evaluated. 252 were ineligible. Ineligibility was determined on the basis of previously documented DVT or pulmonary embolism in 100 patients, contraindication to contrast medium in 21, suspected concurrent pulmonary embolism in 20, pregnancy in 9, prolonged anticoagulant therapy in 4, below-knee amputation in 2, and findings that were not compatible with DVT in 96 (the diagnoses were predominantly musculoskeletal injuries, chronic edema, superficial phlebitis in varicose veins, and arthritis). None of these 96 patients developed symptomatic venous thromboembolic complications

| Checklist |
|---|
| Major points |
| Active cancer (treatment ongoing or within previous 6 months or palliative) |
| Paralysis, paresis, or recent plaster immobilisation of the lower extremities |
| Recently bedridden >3 days and/or major surgery within 4 weeks |
| Localised tenderness along the distribution of the deep venous system |
| Thigh and calf swollen (should be measured) |
| Calf swelling 3 cm >symptomless side (measured 10 cm below tibial tuberosity) |
| Strong family history of DVT (≥2 first degree relatives with history of DVT) |
| Minor points |
| History of recent trauma (≥60 days) to the symptomatic leg |
| Pitting oedema; symptomatic leg only |
| Dilated superficial veins (non-varicose) in symptomatic leg only |
| Hospitalisation within previous 6 months |
| Erythema |
| **Clinical probability** |
| High |
| ≥3 major points and no alternative diagnosis |
| ≥2 major points and ≥2 minor points+no alternative diagnosis |
| Low |
| 1 major point+≥2 minor points+has an alternative diagnosis |
| 1 major point+≥1 minor point+no alternative diagnosis |
| 0 major points+≥3 minor points+has an alternative diagnosis |
| 0 major points+≥2 minor points+no alternative diagnosis |
| Moderate |
| All other combinations |

Active cancer did not include non-melanomatous skin cancer; deep-vein tenderness had to be elicited either in the calf or thigh in the anatomical distribution of the deep venous system.

Table 1: **Clinical model for predicting pretest probability for deep-vein thrombosis**

during the 6 month follow-up. The proportion of ineligible patients and the reasons for ineligibility did not differ between centres. Of the 635 eligible patients, 42 refused consent and venography could not be done or evaluated in 60 patients. In 4 cases, the physician did not complete the data form, and therefore the model could not be evaluated in these patients. Thus, 529 patients were evaluated. Venograms showed thrombosis in 135 (25·5%); 113 (84%) had proximal DVT and 22 (16%) had distal DVT. The prevalence of DVT was 42% (42/101) in Padua, 22% (85/390) at the Henderson General Hospital, and 21% (8/38) at McMaster University Medical Centre (p <0·001).

### *Clinical model*

Of the 529 evaluable patients, 85 (16%) were in the high pretest probability category of whom 72 had DVT (69 proximal), resulting in a prevalence of 85%; 143 (27%) were in the moderate pretest probability category of whom 47 had DVT (34 proximal), resulting in a prevalence of 33%; and 301 (57%) patients were in the low pretest probability category of whom 16 had DVT (10 proximal), resulting in a prevalence of 5%. Thus, 73% of patients were in either the low or high pretest probability categories. The difference in prevalence of DVT in the three categories was statistically significant (p<0·001). The proportion of proximal DVT that involved the distal popliteal vein was determined in the three pretest probability categories: they represented 11·5% (8/69) of DVT in the high pretest probability group, 26% (9/34) in the moderate group, and 30% (3/10) in the low probability group (p=0·08). However, 17 of 86 proximal thrombi at the Henderson Hospital and 3 of 44 in Padua involved the distal popliteal vein (p=0·026). The accuracy of the clinical model was similar in the three participating centres (table 2) despite the higher frequency and greater severity of DVT in Padua. The proportion of calf DVT was 4% (3/72), 28% (13/47), 38% (6/16) in the high, moderate, and low groups, respectively (p<0·01). The weighted Kappa value for the assessment of interobserver reliability, for the clinical model, was 0·85 which represents an excellent level of agreement.[10]

| Patient pretest probability | Frequency of DVT by venography (centre) | | | | |
|---|---|---|---|---|---|
| | Henderson | Padau | McMaster | Total (three centres combined) | p |
| High | 86%, 42/49 | 80%, 24/30 | 100%; 6/6 | 85% (75–92%) | 0·44 |
| Moderate | 29%, 32/109 | 46%, 13/28 | 33%, 2/6 | 33% (35–41%) | 0·23 |
| Low | 4·7%, 11/232 | 12%, 5/43 | 0%, 0/26 | 5% (3–8·5%) | 0·08 |

95% CI in parenthesis, numerator represents number of patients with DVT, denominator the total number of patients with the indicated pretest probability; p-values represents comparison of the frequency in each pretest probability between the centres.

Table 2: **Prevalence of DVT according to the pretest probability derived by the clinical model**

| Mode-derived pretest probability | Sensitivity (proximal) | Sensitivity (all DVT) | Specificity |
|---|---|---|---|
| High | 94% (59/63) | 91% (59/65) | 100% (13/13) |
| Moderate | 83% (25/30) | 61% (25/41) | 99% (86/87) |
| Low | 80% (8/10) | 67% (10/15) | 98% (247/253) |
| p | 0·21 | 0·01 | 0·68 |
| Three groups combined | 89% (92/103) 95% CI 82–95% | 78% (94/121) 95% CI 69–85% | 98% (346/353) 95% CI 96–99% |

p-values are for comparison of the sensitivity and specificity across the three pretest probability categories. Sensitivity was defined as the proportion of people with the disease who have a positive test; specificity was defined as the proportion of people without the disease who have a negative test.

Table 3: **Sensitivity and specificity of ultrasonography for detection of all DVT and proximal DVT in the three pretest probability categories**

### *Accuracy of ultrasonography*

Table 3 shows ultrasonography results in 477 of the 495 (96%) patients. The sensitivity of ultrasonography was 89% (95% CI 82–95%) for proximal DVT and 78% (69–85%) for all DVT, and the specificity for all DVT and proximal DVT was 98% (96–99%). The positive and negative predictive values for proximal DVT were 91% (95% CI, 84% to 96%) and 98% (96% to 99%). Despite the higher prevalence and the greater severity of deep-vein thromboses in Padua there was no difference in sensitivity or specificity of ultrasonography between hospitals (p=0·32 and p=1·0, respectively).

### *Evaluation of ultrasonography combined with clinical assessment*

Within each of the pretest probability categories the sensitivity, specificity, and positive and negative predictive values of ultrasonography was tabulated both for all DVT and proximal DVT. Table 3 shows the sensitivity of ultrasonography for all DVT, which was significantly higher in the high pretest probability category than in the moderate or low categories (p=0·01). The sensitivity of ultrasonography for proximal DVT among the three pretest probability categories, showed a similar trend as

| Ultrasound result | DVT | High PTP | Moderate PTP | Low PTP |
|---|---|---|---|---|
| Abnormal | Total | 100% (59/59) | 96% (25/26) | 63% (10/16) |
| | Proximal | 100% (59/59) | 96% (25/26) | 57% (8/14) |
| Normal | Total | 32% (6/19) | 16% (16/102) | 2% (5/251) |
| | Proximal | 24% (4/17) | 5% (5/93) | <1% (2/248) |

Numerators represent the number of patients with DVT and the denominators the total number of patients with a given ultrasound result.

Table 4: **Post-test probability for all DVT and proximal DVT with normal and abnormal results on ultrasonography in the three pretest probability (PTP) categories**

for all DVT but the differences were not significant (p=0·21). The difference in specificity of ultrasonography in the three pretest categories was not significant (p=0·68).

The post-test probability of all DVT with an abnormal ultrasonography was 100% (94–100%) in the high pretest probability group, 96% (80–100%) in the moderate pretest probability group, but only 63% (29–82%) in the low pretest group. The numbers were essentially the same for proximal DVT (table 4). When the ultrasonography was normal the post-test probability of proximal DVT was 24% (75–50%), 5% (2–12%) and less than 1% (0·1–3%) in the high, moderate, and low pretest probability categories, respectively.

## Discussion

Our findings suggest that the combination of patients' pretest probability for DVT by a clinical model and ultrasonography results can simplify and improve the diagnostic process and challenge the widely held dogma that clinical diagnosis is of no use in the diagnostic assessment of patients with suspected DVT. Physicians were able to use a clinical model to stratify patients with suspected DVT into three distinct pretest probabilities. Reproducibility of the model is suggested by the similar accuracy in the three centres despite the higher prevalence and larger size of DVT in Padua. We evaluated our clinical model and ultrasonography by the standard approach recommended for the evaluation of new diagnostic tests.[11,12] Furthermore, we employed an ultrasonography method that has a very high sensitivity and specificity for proximal DVT in symptomatic patients.[13–15] The interobserver reliability of the model was validated in a subset of patients who were examined independently by two physicians. Previous studies reported that the clinical diagnosis of DVT is inaccurate;[1,2,16,17] however, these reports did not include two of the three essential components of our clinical model—namely, the presence of risk factors for venous thrombosis and the probability that the clinical features are likely to be caused by other disorders that mimic DVT.

The accuracy of ultrasonography may have differed according to the pretest probability for DVT because the proportions of large and small proximal thrombi, and calf vein thrombi were different in the three groups. The observation that the sensitivity of ultrasonography varied with the pretest probability for DVT has not been described in symptomatic patients but is plausible. Thus, patients with minimal symptoms who had less extensive thrombi were concentrated in the low pretest probability group, whereas those with overt symptoms and signs and more extensive thrombi were clustered in the high probability group. The notion that ultrasonography is less sensitive to less extensive thrombi is supported by data from studies that assessed ultrasound screening for DVT in postoperative patients.[18–20]

It has been recommended[4] that symptomatic patients with abnormal noninvasive test results should be treated for DVT, whereas those with normal test results should have the noninvasive test repeated twice in 7 days to detect extending calf-vein thrombi. Our findings suggest that this approach would be appropriate for patients with a moderate pretest probability but it should be modified in two circumstances. These are when the pretest probabilities and noninvasive test results are discordant and when the noninvasive test is normal in patients with a low pretest probability (figure 1). In the event of discordant results, the false-negative rate with ultrasonography is substantial in patients with high clinical probabilities and therefore a normal ultrasound result should be confirmed with venography. If this approach were taken in our study, venography would be required in less than 20% of patients in the high pretest probability category. Conversely, since the false-positive rate with ultrasonography was substantial in patients with low clinical probabilities, it would be prudent to confirm the abnormal test result with venography to avoid unnecessary treatment. By contrast, a normal ultrasound result in patients with low pretest probability reliably excludes a diagnosis of DVT, so that patients can be excluded from serial testing. The serial testing strategy is costly because most patients who return for repeat testing do not have DVT.[5,21–23] Since 55% of patients investigated had a low pretest probability and a normal ultrasound result, a substantial number could be excluded from serial testing by combining clinical diagnosis with ultrasound results; costs could be reduced significantly. We caution that although the clinical model is not complex and the data form can be completed in less than 2 minutes, the examining physician should use a check sheet to ensure it is done properly.

In conclusion, the combination of pretest probability with noninvasive diagnostic test results has the potential to simplify and improve the diagnostic process in patients with suspected DVT, and to decrease cost. A prospective validation study is needed to test the safety and clinical utility of the clinical model.

Dr Wells was a recipient of a McLaughlin Scholarship from the University of Ottawa at the time of this study. Dr Anderson is a research fellow of the Heart and Stroke Foundation of Canada. Dr Weitz is a career investigator of the Heart and Stroke Foundation of Ontario. Dr Hirsh is a distinguished research professor of the Heart and Stroke Foundation of Canada and is a Trillium Award recipient from the Ontario Ministry of Health. Dr Ginsberg is a recipient of a research scholarship from the Heart and Stroke Foundation of Canada. We thank Mrs J Cole, Mrs S Smale, Ms D Redshaw, and Mrs L Harrison for their enthusiastic assistance.

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# Reduced seroconversion to measles in infants given vitamin A with measles vaccination

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## Summary

Administration of 100 000 IU vitamin A at the time of measles immunisation is currently recommended for infants in developing countries. However, the safety and value of giving vitamin A, a potent immune enhancer, with live measles virus vaccines are unknown. We conducted a randomised, double-blind, placebo-controlled clinical trial in Indonesia to evaluate the effect of simultaneous vitamin A supplementation on the immune response to measles immunisation at six months of age.

336 infants received either vitamin A (100 000 IU) or placebo when immunised with standard-titre Schwarz measles vaccine. 82% of infants seroconverted to measles. In a multiple logistic regression model adjusting for maternal antibody titres, vitamin A supplementation was associated with a lower likelihood of seroconversion to measles (odds ratio 0·40, 95% CI 0·19–0·88), and girls were less likely to seroconvert than boys (0·34, 0·15–0·76).

Immunisation with standard-titre Schwarz vaccine at six months of age in this study population is characterised by high seroconversion rates. However, simultaneous high-dose vitamin A may interfere with seroconversion to live measles vaccine in infants with maternal antibody.

*Lancet* 1995; **345:** 1330–32

*See Commentary page 1317*

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## Introduction

Vitamin A deficiency remains a major cause of childhood morbidity and mortality in many developing countries. Regular vitamin A supplementation has been recommended for children aged six months and older to improve survival.[1] Because child immunisation programmes involve more than 500 million contacts per year in developing countries, it has been suggested that the infrastructure of these programmes could be used to deliver vitamin A supplements.[2] Administration of 100 000 IU vitamin A at the time of measles immunisation is currently recommended for infants aged six and nine months.[3] Vitamin A is a potent immune enhancer and has long been known as the "anti-infective" vitamin.[4] The safety and value of linking vitamin A delivery with live measles virus vaccines as a potential means of enhancing immunisation are unknown. We conducted a randomised, double-blind, placebo-controlled clinical trial to determine the effect of simultaneous vitamin A administration on antibody responses to measles vaccination.

## Subjects and methods

The study population consisted of six-month-old infants in 19 villages in the Bogor District, West Java, Indonesia. This area has a high prevalence of subclinical vitamin A deficiency (>50% of infants with serum retinol <0·7 μmol/L, unpublished) and is typical of rural, rice-based agricultural areas of southeast Asia. Births were monitored in the study area with the assistance of the rural health centres. Between December, 1992, and March, 1993, standard-titre Schwarz measles vaccine, 0·5 mL (Morbilivax, lot 68AO9, 4·13 $\log_{10}$ median tissue-culture infectious doses [$TCID_{50}$] per dose, Biocine Sclavo, Siena, Italy), was administered at six months of age by two paediatricians. Vitamin A, 100 000 IU, or placebo in identical capsules (Task Force Sight and Life, Basel, Switzerland) was given orally at the same time as measles immunisation. Infants received identification numbers as they were enrolled in the study, and each identification number had an envelope with an identical capsule containing either vitamin A or placebo. At the time of treatment allocation, both