

- 4 De Lorgeril M, Renaud S, Mamelle N, Salen P, Martin JL, Monjaud I, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 1994;343:1454-9.
- 5 Singh RB, Dubnov G, Niaz MA, Ghosh S, Singh R, Rastogi SS, et al. Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean diet heart study): a randomised single-blind trial. *Lancet* 2002;360:1455-61.
- 6 Willett WC, Sacks F, Trichopoulos A, Drescher G, Ferro-Luzzi A, Helsing E, et al. Mediterranean diet pyramid: a cultural model for healthy eating. *Am J Clin Nutr* 1995;61(suppl 6):S1402-6.
- 7 Trichopoulou A, Kouris-Blazos A, Wahlqvist ML, Gnardellis C, Lagiou P, Polychronopoulos E, et al. Diet and overall survival in elderly people. *BMJ* 1995;311:1457-60.
- 8 Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to Mediterranean diet and survival in a Greek population. *N Engl J Med* 2003;348:2599-608.
- 9 Osler M, Schroll M. Diet and mortality in a cohort of elderly people in a north European community. *Int J Epidemiol* 1997;26:155-9.
- 10 Lasheras C, Fernandez S, Patterson AM. Mediterranean diet and age with respect to overall survival in institutionalised, nonsmoking elderly people. *Am J Clin Nutr* 2000;71(4):987-92.
- 11 Knuops KT, de Groot LC, Kromhout D, Perrin AE, Moreiras-Varela O, Menotti A, et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. *JAMA* 2004;292:1433-9.
- 12 Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, et al. European prospective investigation into cancer and nutrition (EPIC): study populations and data collection. *Public Health Nutr* 2002;5:1113-24.
- 13 Slimani N, Kaaks R, Ferrari P, Casagrande C, Clavel-Chapelon F, Lotze G, et al. European prospective investigation into cancer and nutrition (EPIC) calibration study: rationale, design and population characteristics. *Public Health Nutr* 2002;5:1125-45.
- 14 Kaaks R, Riboli E. Validation and calibration of dietary intake measurements in the EPIC project: methodological considerations. European prospective investigation into cancer and nutrition. *Int J Epidemiol* 1997;26(suppl 1):S15-25.
- 15 Margetts BM, Pietinen P. European prospective investigation into cancer and nutrition: validity studies on dietary assessment methods. *Int J Epidemiol* 1997;26(suppl 1):S1-5.
- 16 Deharveng G, Charrondiere UR, Slimani N, Southgate DA, Riboli E. Comparison of nutrients in the food composition tables available in the nine European countries participating in EPIC. European prospective investigation into cancer and nutrition. *Eur J Clin Nutr* 1999;53:60-79.
- 17 James WPT, Schofield EC. *Human energy requirements: a manual for planners and nutritionists*. Oxford: Oxford University Press, 1990.
- 18 Department of Health. Dietary reference values for food energy and nutrients for the United Kingdom. *UK Department of Health report on health and social subjects No 41*. London: Stationery Office, 1991.
- 19 Breslow NE, Day NE. *Statistical methods in cancer research. Vol II. The design and analysis of cohort studies*. Lyons: International Agency for Research on Cancer, 1987. (IARC scientific publication No 82.)

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Use of clinical syndromes to target antibiotic prescribing in seriously ill children in malaria endemic area: observational study

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Abstract

Objectives To determine how well antibiotic treatment is targeted by simple clinical syndromes and to what extent drug resistance threatens affordable antibiotics.

Design Observational study involving a priori definition of a hierarchy of syndromic indications for antibiotic therapy derived from World Health Organization integrated management of childhood illness and inpatient guidelines and application of these rules to a prospectively collected dataset.

Setting Kilifi District Hospital, Kenya.

Participants 11 847 acute paediatric admissions.

Main outcome measures Presence of invasive bacterial infection (bacteraemia or meningitis) or *Plasmodium falciparum* parasitaemia; antimicrobial sensitivities of isolated bacteria.

Results 6254 (53%) admissions met criteria for syndromes requiring antibiotics (sick young infants; meningitis/encephalopathy; severe malnutrition; very severe, severe, or mild pneumonia; skin or soft tissue infection): 672 (11%) had an invasive bacterial infection (80% of all invasive bacterial infections identified), and 753 (12%) died (93% of all inpatient deaths). Among *P falciparum* infected children with a syndromic indication for parenteral antibiotics, an invasive bacterial infection was detected in 4.0-8.8%. For the syndrome of meningitis/encephalopathy, 96/123 (76%) isolates were fully sensitive in vitro to penicillin or chloramphenicol.

Conclusions Simple clinical syndromes effectively target children admitted with invasive bacterial infection and those at risk of death. Malaria parasitaemia does not justify withholding empirical parenteral antibiotics. Lumbar puncture is critical to the rational use of antibiotics.

Introduction

Invasive bacterial infections are an important cause of childhood illness and death worldwide. Advice on the management of common conditions in resource poor countries has recently been summarised by the World Health Organization.¹ Diagnosis in such settings usually depends on the identification of a small number of clinical syndromes. Seriously ill children often meet criteria for several clinical syndromes, however, and different diseases may cause the same clinical syndrome.² In malaria endemic areas the clinical manifestations of malaria overlap with those of pneumonia, bacteraemia, and meningitis.

We aimed to determine how well antibiotic treatment is targeted by simple rules based on current WHO guidelines, how application of such rules is affected by malaria parasitaemia in an endemic area, and to what extent antibiotic resistance threatens the use of cheap antibiotics.

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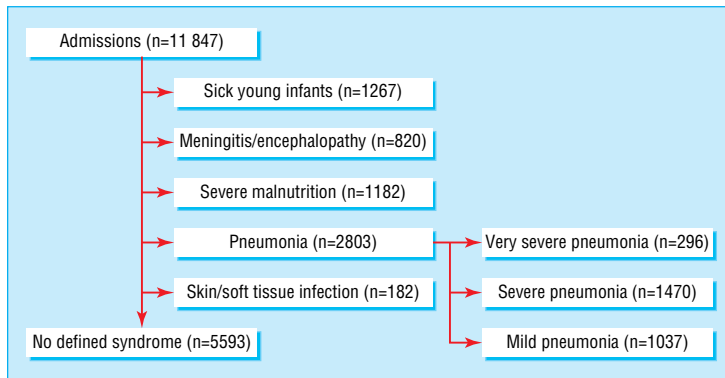
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Hierarchical classification of defined syndromes requiring antibiotic treatment

Methods

Location and clinical methods

Kilifi District Hospital is located in a rural area on the Kenyan coast. Children receive up to 50 mosquito bites infective for *Plasmodium falciparum* annually, with two transmission seasons.³ Ten per cent of women attending the hospital antenatal clinic in 2000 were infected with HIV.⁴ *Haemophilus influenzae* type b conjugate vaccination had not begun at the time of the study.

We recruited all children admitted from February 1999 to December 2001, unless no diagnostic uncertainty existed. We collected clinical data, a malaria slide, full blood count, and blood culture on admission. Table 1 gives clinical definitions. Our lumbar puncture policy included any of the following at any time during admission: meningism; impaired consciousness (delayed until neurologically stable); prostration in children aged under 3 years; seizures, other than simple febrile seizures; or as a septic screen in young infants.⁵ Inpatient treatment followed WHO and local guidelines, including recommended protocols for severe malnutrition.¹ See bmj.com for details of laboratory methods.

Analysis

We classified children as meeting the definition of a syndrome warranting antibiotic treatment or not by using data collected on admission. We constructed an a priori hierarchy of the syndromes, reflecting prioritisation in clinical practice (figure). We assigned individual children to their highest priority syndrome. We explored the possibility that antibiotic resistance increased the risk of inpatient death by using multiple

logistic regression. We labelled individuals as “resistant to treatment” if the organism isolated was resistant in vitro to the antibiotics defined by their syndrome.

Results

Among 14 987 admissions, we analysed 11 847 admissions after exclusions (see bmj.com). We detected an invasive bacterial infection in 843 (7.1%) admissions (table 2): 633 (5.3%) positive blood culture only, 9 (<0.1%) positive cerebrospinal fluid (CSF) culture only, 111 (0.9%) positive blood and CSF cultures, 21 (0.2%) positive blood culture with CSF evidence of meningitis, and 69 (0.6%) CSF evidence of meningitis but negative cultures. We detected *P. falciparum* parasitaemia in 5270 (45%) admissions. A defined syndrome requiring antibiotics was present in 6254 (53%) admissions; of these, 672 (11%) had an invasive bacterial infection, representing 80% of all invasive bacterial infections, and 753 (12%) died in hospital, representing 93% of 813 inpatient deaths. See table on bmj.com for details of in vitro antimicrobial susceptibilities.

Sick young infants

Of 1267 young infants, 184 (15%) had an invasive bacterial infection (table 2), principally group B streptococci, *Escherichia coli*, *Acinetobacter*, and *Klebsiella* spp. The proportion of isolates susceptible in vitro to ampicillin-gentamicin was greater than that resistant to either penicillin-gentamicin or cefotaxime (both $P=0.001$).

Meningitis/encephalopathy syndrome

This clinical syndrome captured 101/160 (63%) cases of laboratory defined meningitis in children at least 60 days old; 21 (13%) other cases of meningitis outside this syndrome definition met another syndrome definition indicating parenteral antibiotics. The remaining 38 (24%) cases of meningitis would not have initially received parenteral antibiotics if syndromic treatment rules (that do not rely on lumbar puncture) had been followed absolutely. The most common isolates were *Streptococcus pneumoniae* and *H. influenzae*. Four hundred and twenty two (52%) children with this syndrome had a positive malaria slide; 29 (6.9%) of these had an invasive bacterial infection compared with 117/397 (30%) children with negative slides ($P<0.001$, table 2). Case fatality did not vary significantly with malaria parasitaemia. Only 76% of isolates were fully sensitive in vitro to penicillin-

Table 1 Definition of clinical syndromes and currently recommended antibiotic treatment

Syndrome	Definition	Recommended antibiotic treatment*
Sick young infants	Any child <60 days old sick enough to warrant admission to hospital	Gentamicin with either penicillin or ampicillin
Meningitis/encephalopathy	Neck stiffness, bulging fontanel, or impaired consciousness†	Penicillin with chloramphenicol
Severe malnutrition	Severe wasting‡ or kwashiorkor	Gentamicin with either penicillin or ampicillin
Very severe pneumonia	Respiratory distress§ plus one or more of prostration¶, cyanosis, or hypoxia**	Chloramphenicol
Severe pneumonia	Respiratory distress§	Penicillin
Mild pneumonia	Tachypnoea†† plus a history of either cough or difficulty breathing	Oral amoxicillin
Skin or soft tissue infection	Cellulitis, abscess, pyomyositis	Cloxacillin

*Parenteral unless otherwise indicated.

†Blantyre coma score ≤ 2 .

‡Weight for age z score < -4 by NCHS standards (Epi Info 2000, CDC, Atlanta, USA).

§Lower chest wall indrawing or abnormally deep breathing.

¶Inability to sit unassisted if aged ≥ 1 year or inability to drink or breastfeed if aged < 1 year.⁶

** $\text{SaO}_2 < 90\%$ in air by pulse oximetry (Nellcor, USA).

†† ≥ 50 breaths per minute if aged 60 days to 1 year; ≥ 40 breaths per minute if ≥ 1 year old.¹

Table 2 Number of admissions with defined syndromes, prevalence of invasive bacterial infections, malaria parasitaemia, and outcome. Values are numbers (percentages) unless stated otherwise

Syndrome	Median (IQR) age (months)	Invasive bacterial infection*	Meningitis	Deaths	Malaria slide positive	Invasive bacterial infection*	
						Malaria positive	Malaria negative
Sick young infants (n=1267)	7 (2-22) days	184 (15)	50 (4.0)	280 (22)	34 (2.7)	2/34 (5.9)	176/1213 (15)
Meningitis/encephalopathy (n=820)	27 (13-46)	147 (18)	101 (12)	150 (18)	422 (52)	29/422 (6.9)	117/397 (30)
Severe malnutrition (n=1182)	24 (15-39)	141 (12)	3 (0.3)	200 (17)	376 (32)	33/376 (8.8)	108/802 (13)
Very severe pneumonia (n=296)	13 (5-29)	33 (11)	8 (2.7)	56 (19)	124 (42)	5/124 (4.0)	28/172 (16)
Severe pneumonia (n=1470)	10 (5-20)	88 (6.0)	5 (0.3)	52 (3.5)	455 (31)	18/455 (4.0)	69/1004 (6.9)
Mild pneumonia (n=1037)	17 (10-29)	69 (6.7)	8 (0.8)	15 (1.5)	526 (51)	16/526 (3.0)	52/509 (10)
Skin/soft tissue infection (n=182)	19 (10-36)	10 (5.5)	0	0	86 (47)	1/86 (1.2)	9/95 (9.5)
No defined syndrome (n=5593)	23 (11-44)	171 (3.1)	35 (0.6)	60 (1.1)	3247 (58)	53/3247 (1.6)	118/2324 (5.1)
All admissions (n=11 847)	17 (7-35)	843 (7.1)	210 (1.8)	813 (6.9)	5270 (45)	157/5270 (3.0)	677/6516 (10)

IQR=interquartile range.

*Includes meningitis and bacteraemia.

chloramphenicol compared with 93% for cefotaxime ($P < 0.001$). When we excluded *H influenzae*, 86% of isolates were sensitive to penicillin-chloramphenicol. Susceptibility results were similar when all meningitis cases missed by this syndrome definition were included.

Severe malnutrition syndrome

Severe malnutrition syndrome accounted for 141/659 (21%) of invasive bacterial infections and 200/533 (38%) of deaths in children aged at least 60 days (table 2). *S pneumoniae*, *E coli*, and non-typhoidal salmonellae were the most common isolates. Most (959, 81%) of these admissions did not meet criteria for another syndrome requiring antibiotics, making anthropometry or kwashiorkor the sole basis for antibiotic treatment. Of these, 88 (9.2%) had an invasive bacterial infection and 153 (16%) died, compared with 53 (24%) and 47 (21%) of the 223 who met other syndrome definitions (both $P < 0.001$). The prevalence of invasive bacterial infection was higher in children with negative malaria slides than in those with positive slides ($P = 0.02$, table 2). Case fatality was lower in admissions with negative malaria slides (166/802, 21%) than in those with positive slides (34/376, 9.0%) ($P < 0.001$). In vitro susceptibility to amoxicillin-gentamicin was greater than that to penicillin-gentamicin ($P < 0.05$).

Pneumonia syndromes

Of 2803 (24%) children admitted with a pneumonia syndrome, 1470 (52%) had severe disease and 296 (11%) had very severe disease. The prevalence of invasive bacterial infection with severe pneumonia syndrome was similar to that with mild pneumonia syndrome, but case fatality was greater ($P = 0.001$, table 2). *S pneumoniae* (38%), Enterobacteriaceae (30%), and *H influenzae* (15%) were the most common isolates. Three to four per cent of children with a positive malaria slide had an invasive bacterial infection compared with 6.9-16% in those with a negative slide (all $P < 0.001$, table 2). Case fatality did not vary significantly with malaria parasitaemia. Isolates from children with severe or very severe pneumonia were more commonly susceptible to chloramphenicol alone than to penicillin alone ($P = 0.05$) and to ampicillin-gentamicin than to penicillin-gentamicin ($P = 0.04$).

Skin or soft tissue infection syndrome

Ten (5.5%) of 182 children with skin or soft tissue infections had an invasive bacterial infection. *Staphylo-*

coccus aureus accounted for four (40%) invasive infections, and all these were sensitive to cloxacillin.

No defined syndrome requiring antibiotics

Of 5593 children without a syndrome requiring antibiotics, 171 (3.1%) had an invasive bacterial infection and 60 (1.1%) died. Non-typhoidal salmonellae, *S pneumoniae*, and *S aureus* were the most common isolates. Of 2324 malaria slide negative admissions, 118 (5.1%) had an invasive bacterial infection compared with 53/3247 (1.6%) slide positive admissions ($P < 0.001$). Among children with an axillary temperature $\geq 39^\circ\text{C}$, invasive bacterial infection was present in 47/488 (9.6%) with a negative malaria slide compared with 22/1422 (1.6%) with a positive slide ($P < 0.001$). We found no significant association between invasive bacterial infection and prostration, seizures, diarrhoea, vomiting, jaundice, or severe anaemia. Among children with an invasive bacterial infection, 0/53 children with a positive malaria slide died compared with 11/118 (9.3%) of those with a negative slide ($P = 0.02$). In those without an invasive bacterial infection, 20/3194 (0.6%) children with a positive malaria slide died compared with 29/2216 (1.3%) with a negative slide ($P = 0.009$).

Antimicrobial resistance and outcome

Antibiotic resistance to recommended treatment was associated with an odds ratio of 1.22 (95% confidence interval 0.78 to 1.92) for fatal outcome. If only deaths after 24 hours of admission were examined, the association with a fatal outcome strengthened (odds ratio = 1.90, 0.95 to 3.80), but the possibility of no association could not be absolutely excluded.

Discussion

Syndromic rules effectively target children with invasive bacterial infections

Among acute paediatric admissions to a Kenyan district hospital, simple clinical syndromes based on WHO guidelines identified at admission 80% of children with an invasive bacterial infection and 93% of subsequent inpatient deaths. For every nine children with a defined syndrome indicating antibiotic treatment, one child had an identified invasive bacterial infection. Given the likely insensitivity of blood culture, we think this justifies empirical antibiotic treatment.

Does a positive malaria slide justify withholding antibiotics?

Overall, the presence of *P falciparum* parasitaemia was associated with a lower risk of invasive bacterial infection. However, where a syndrome requiring parenteral antibiotics was present, children with a positive malaria slide still had a risk of detectable invasive bacterial infection between 1 in 25 and 1 in 11 and a risk of dying between 1 in 28 and 1 in 6. We believe that these risks are too high to justify withholding parenteral antibiotics because a malaria slide is positive.

For children with the syndrome of mild pneumonia and a positive malaria slide, the case for withholding antibiotics strengthens: within this group, 1 in 33 had an identified invasive bacterial infection and 1 in 66 died. Given that blood cultures are less sensitive than other tests such as lung aspiration,^{6,7} that treatment with oral amoxicillin is relatively inexpensive, and that the overall potential antibiotic pressure on resistance exerted by this group would be small, dual treatment of children in hospital seems justified.

Recent reports suggest that the reading of malaria slides in the region is commonly unreliable, with frequent false positives.^{8,9} Among children with a clinical syndrome compatible with cerebral malaria, such false positives would have a 1 in 3 chance of invasive bacterial infection. Children with the mild pneumonia syndrome and a false positive malaria slide would have a 1 in 10 chance. The unreliability of malaria microscopy in practice further considerably strengthens the case for following syndromic indications for antibiotic treatment, irrespective of the malaria slide result.

Among those with an axillary temperature $\geq 39^{\circ}\text{C}$ but without a defined syndromic indication for antibiotics, an accurate malaria slide may be helpful in deciding on antibiotic treatment: 1 in 10 of those with a negative malaria slide had an "occult" invasive bacterial infection, whereas invasive bacterial infection was rare in children with positive slides and the outcome significantly better, although we did not establish how many of these children actually received antibiotics.

Does a syndrome indicating antibiotic treatment justify withholding antimalarials?

A third of children with a syndrome requiring antibiotics had a *P falciparum* parasitaemia, and 24% of the deaths in this group were due to malaria in the absence of invasive bacterial infection. Thus, among children admitted to hospital, suspected or microscopically confirmed malaria should be treated with antimalarials regardless of any antibiotic treatment. Where the results of a malaria slide are unreliable, children with features of severe malaria (impaired consciousness, deep breathing, or both) should receive both parenteral antimalarials and antibiotics. Oral antimalarials are likely to be adequate for those not classified as severe.

Meningitis: problems with clinical diagnosis and antimicrobial resistance

One in four cases of meningitis presented without a clinical syndrome indicating parenteral antibiotic treatment. Results were similar when more detailed clinical indicators of meningitis were studied in this hospital.¹⁰ Meningitis was identified because our

What is already known on this topic

Local data on bacterial aetiology and antimicrobial susceptibilities of childhood diseases are sparse in sub-Saharan Africa

Treatment guidelines for children in this setting tend to focus on individual diseases, which may lead to uncertainty where several possible causes of illness exist

The clinical manifestations of severe malaria overlap with those of invasive bacterial infection, and malaria microscopy may be unreliable, causing further uncertainty

What this study adds

A simple hierarchical classification of clinical syndromes seems to effectively target admissions with invasive bacterial infection and those at risk of death

A positive malaria slide does not seem to justify withholding parenteral antibiotic treatment where it is indicated by a syndrome requiring antibiotics

A practical approach is to make separate decisions regarding antibiotic, antimalarial, and other treatments on the basis of the presence of defined clinical syndromes and the results of any reliable laboratory investigations

lumbar puncture protocol was broader than the syndrome definition. The pivotal role of lumbar puncture in rationalising treatment underlines the need to improve its use⁵: 88% of children with the syndrome did not have meningitis. Lumbar puncture therefore permits considerable cost savings, especially where there is significant resistance to inexpensive antibiotics.¹¹ The high sensitivity to amoxicillin-gentamicin associated with this syndrome reflects the proportion of children with bacteraemia but not meningitis.

Conclusions

Simple rules based on a hierarchical classification of WHO integrated management of childhood illness clinical syndromes can target admissions with invasive bacterial infections and those at risk of death. The antibiotic management of children admitted to hospital in settings with no or few diagnostic resources should reflect a comprehensive assessment of the sick child and not focus on single diseases (see checklist on bmj.com). Our data are limited by being from one district hospital and using *in vitro* susceptibility testing. Similar studies are needed from other areas, especially those with different prevalences of malaria and HIV.

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- 1 World Health Organization. *Management of the child with a serious infection or severe malnutrition: guidelines at the first referral level in developing countries*. Geneva: WHO, 2000.
- 2 English M, Berkley J, Mwangi I, Mohammed S, Ahmed M, Osier F, et al. Hypothetical performance of syndrome-based management of acute paediatric admissions of children aged more than 60 days in a Kenyan district hospital. *Bull WHO* 2003;81:166-73.
- 3 Mbogo CM, Mwangangi JM, Nzovu J, Gu W, Yan G, Gunter JT, et al. Spatial and temporal heterogeneity of Anopheles mosquitoes and Plasmodium falciparum transmission along the Kenyan coast. *Am J Trop Med Hyg* 2003;68:734-42.
- 4 Ministry of Health, Republic of Kenya. *AIDS in Kenya*. 6th ed. Nairobi: Government of Kenya, 2001.

- 5 Berkley JA, Mwangi I, Mwarumba S, Lowe B, Marsh K, Newton CRJC. Diagnosis of acute bacterial meningitis in children at a district hospital in sub-Saharan Africa. *Lancet* 2001;357:1753-7.
- 6 Falade AG, Mulholland EK, Adegbola RA, Greenwood BM. Bacterial isolates from blood and lung aspirate cultures in Gambian children with lobar pneumonia. *Ann Trop Paediatr* 1997;17:315-9.
- 7 Falade AG, Adegbola RA, Mulholland EK, Greenwood BM. Respiratory rate as a predictor of positive lung aspirates in young Gambian children with lobar pneumonia. *Ann Trop Paediatr* 2001;21:293-7.
- 8 Makani J, Matuja W, Liyombo E, Snow RW, Marsh K, Warrell DA. Admission diagnosis of cerebral malaria in adults in an endemic area of Tanzania: implications and clinical description. *Q J Med* 2003;96:355-62.
- 9 Reyburn H, Mbatia R, Drakeley C, Carneiro I, Mwakasungula E, Mwerinde O, et al. Overdiagnosis of malaria in patients with severe febrile illness in Tanzania: a prospective study. *BMJ* 2004;329:1212.
- 10 Berkley JA, Versteeg AC, Mwangi I, Lowe BS, Newton CR. Indicators of acute bacterial meningitis in children at a rural Kenyan district hospital. *Pediatrics* 2004;114:e713-9.
- 11 Duke T, Micheal A, Mokele D, Wal T, Reeder J. Chloramphenicol or ceftriaxone, or both, as treatment for meningitis in developing countries. *Arch Dis Child* 2003;88:536-9.

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Opportunity cost of antidepressant prescribing in England: analysis of routine data

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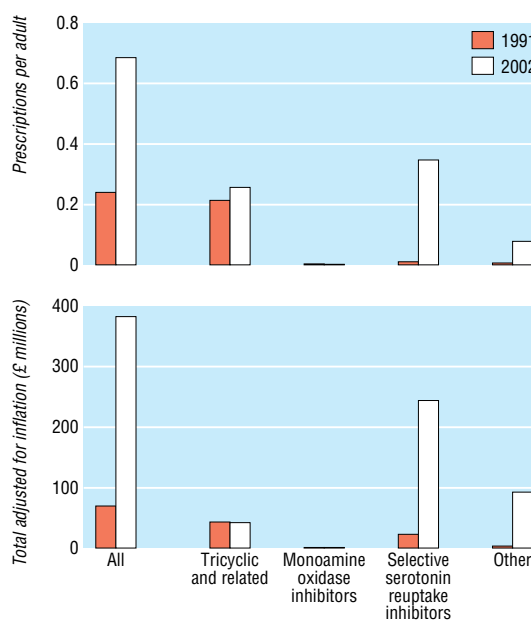
Recently, prescribing of antidepressant drugs has increased exceptionally.¹ At the same time, concerns have been raised about the medicalisation of human distress and, more recently, about the safety of antidepressants.¹

Many general practitioners would like to refer patients for psychological treatment, for which there is good evidence of effectiveness,² but are constrained by the lack of NHS therapists. We estimated the opportunity cost of the recent rise in antidepressant prescribing by valuing it in terms of an effective alternative treatment—cognitive behaviour therapy.

Methods and results

We used Department of Health data on the number and cost of antidepressant drugs dispensed in the community in England to quantify the changes between 1991 and 2002. The baseline year (1991) was chosen to ensure a meaningful timescale and to cover a period of consistent approaches to recording. We took population statistics from www.statistics.gov.uk/statbase, and applied an inflation rate of 32% (from www.statistics.gov.uk/rpi) to 1991 costs.

We estimated the number of patients that could have been treated using cognitive behaviour therapy in 2002, had the rise in prescribing not occurred and the associated costs been diverted to psychological treatment and therapists. We costed the time of a clinical psychologist, including supervision (total equivalent £40 168 (\$74 883; €57 738) full time a year).³ We estimated that each therapist could treat six patients a day for 40 weeks a year and that a treatment episode for mild or moderate depression would comprise six sessions.³ We did a limited sensitivity analysis assuming that graduate mental health workers (£25 475 a year) rather than psychologists provided treatment and that treatment episodes consisted of 18 sessions in line with



Source: Department of Health

Prescriptions per head and total cost of antidepressants in England, 1991-2002

the National Institute for Clinical Excellence's recommendation for moderate or severe depression.²

Between 1991 and 2002, prescriptions per head for all antidepressants increased 2.8-fold and the total cost (adjusted for inflation) increased by £310m; the increase was almost entirely due to selective serotonin reuptake inhibitors (figure). These costs could have

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