Diagnostic value of clinical features at presentation to identify serious infection in children in developed countries: a systematic review

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Summary

Background Our aim was to identify which clinical features have value in confirming or excluding the possibility of serious infection in children presenting to ambulatory care settings in developed countries.

Methods In this systematic review, we searched electronic databases (Medline, Embase, DARE, CINAHL), reference lists of relevant studies, and contacted experts to identify articles assessing clinical features of serious infection in children. 1939 potentially relevant studies were identified. Studies were selected on the basis of six criteria: design (studies of diagnostic accuracy or prediction rules), participants (otherwise healthy children aged 1 month to 18 years), setting (ambulatory care), outcome (serious infection), features assessed (assessable in ambulatory care setting), and sufficient data reported. Quality assessment was based on the Quality Assessment of Diagnostic Accuracy Studies criteria. We calculated likelihood ratios for the presence (positive likelihood ratio) or absence (negative likelihood ratio) of each clinical feature and pre-test and post-test probabilities of the outcome. Clinical features with a positive likelihood ratio of more than 5·0 were deemed red flags (ie, warning signs for serious infection); features with a negative likelihood ratio of less than 0·2 were deemed rule-out signs.

Findings 30 studies were included in the analysis. Cyanosis (positive likelihood ratio range 2·66–52·20), rapid breathing (1·26–9·78), poor peripheral perfusion (2·39–38·80), and petechial rash (6·18–83·70) were identified as red flags in several studies. Parental concern (positive likelihood ratio 14·40, 95% CI 9·30–22·10) and clinician instinct (positive likelihood ratio 23·50, 95 % CI 16·80–32·70) were identified as strong red flags in one primary care study. Temperature of 40°C or more has value as a red flag in settings with a low prevalence of serious infection. No single clinical feature has rule-out value but some combinations can be used to exclude the possibility of serious infection—for example, pneumonia is very unlikely (negative likelihood ratio 0·07, 95% CI 0·01–0·46) if the child is not short of breath and there is no parental concern. The Yale Observation Scale had little value in confirming (positive likelihood ratio range 1·10–6·70) or excluding (negative likelihood ratio range 0·16–0·97) the possibility of serious infection.

Interpretation The red flags for serious infection that we identified should be used routinely, but serious illness will still be missed without effective use of precautionary measures. We now need to identify the level of risk at which clinical action should be taken.

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Introduction

Serious infection is an important cause of morbidity and mortality in children in developed countries. Infections account for 20% of childhood deaths in England, Wales, and Northern Ireland, with the greatest number in children aged 1–4 years.[1] These serious illnesses need to be distinguished from self-limiting acute illnesses that are very common in children. A Dutch survey of parents reported that during a 3-week period, 60% of children had an acute illness episode and 4% had febrile illness.[2] In the UK, acute infections result in 4·0 consultations per person-year in children aged less than 1 year, and 1·3 consultations per person-year in children aged 1–15 years.[3] Additionally, febrile illness accounts for 20% of all visits to the paediatric emergency department.[4]

An early and accurate diagnosis of serious infection in children is essential to reduce morbidity and mortality. However, diagnosis is not straightforward because of the low prevalence of serious illness, and even those few children with serious illness can present at an early stage when the severity of the illness is not apparent. In a primary care setting, less than 1% of children assessed will have a serious illness[5] and there is a duty on the clinician to reassure anxious parents of healthy children and to diagnose seriously ill children.[6] Triage might need to be done rapidly in a pressured environment or by telephone, and by staff who might have limited paediatric experience. Consequently, the diagnosis could be missed at first contact,[7] sometimes with serious consequences.[8]

Panel: Criteria for selection of studies

Design
Studies that assessed diagnostic accuracy or derived prediction rules were selected. Narrative reviews, letters, editorials, comments, and case series of less than 20 patients were excluded. Systematic reviews and meta-analyses were used only as a source of references.

Participants
Studies needed to include children aged between 1 month and 18 years. Studies that included children above or below this age range were selected if they reported age-stratified analyses (so that children aged <1 month or >18 years could be excluded) or if the proportion of children out of range was less than 50%. Studies in children with pre-existing immune suppression (such as HIV infection or neutropenia due to chemotherapy) were excluded.

Setting
Studies in ambulatory care settings (defined as general or family practice, paediatric outpatient clinics, paediatric assessment units, or emergency departments) were selected. Studies done in developing countries were excluded because of the different range of diseases and more advanced stage of disease at presentation. We used the United Nations list to define developed countries, which include Europe, Canada, the USA, Australia, New Zealand, and Japan.

Outcome
Studies that assessed serious infection were selected. Serious infection was defined as sepsis (including bacteraemia), meningitis, pneumonia, osteomyelitis, cellulitis, gastroenteritis with dehydration, complicated urinary tract infection (positive urine culture and systemic effects such as fever), and viral respiratory tract infections complicated by hypoxia (eg, bronchiolitis).

Diagnostic features
Studies that assessed possible triage tests in ambulatory care were selected. Imaging, invasive tests (such as lumbar puncture or joint aspiration), and microbiological tests were not considered; studies reporting laboratory tests available for near-patient testing were selected (although not reported here).

Data reporting
Studies were selected if reconstruction of the two-by-two tables was possible.

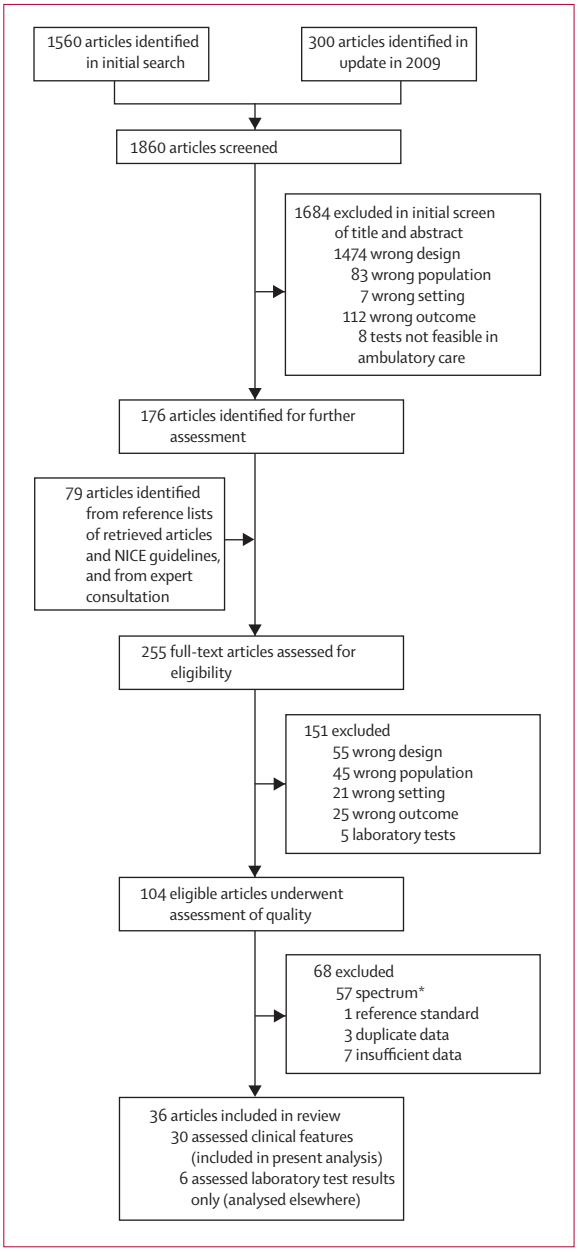

***Figure 1*: Flow diagram for selection of studies**
Only the first reason for exclusion (as ordered in the panel) is reported. NICE=National Institute for Health and Clinical Excellence. *Patient population not representative of patients in clinical practice.

Our attempts to draw up guidance for clinicians in the UK, Belgium, and the Netherlands showed scarcity of evidence on the diagnosis and management of children presenting with acute illness. WHO has sponsored large-scale studies in resource-poor countries[9,10] that provide evidence relevant to those settings; however, in developed countries the evidence base seems more limited and fragmented, and the range of diseases is different. The very low prevalence of serious disease also increases the diagnostic challenge. Therefore, we undertook a systematic review of the evidence from developed countries to identify which clinical features have value in confirming or excluding the possibility of serious infection in children presenting to ambulatory care settings.

Methods

Search strategy and selection criteria

We searched four electronic databases (Medline, Embase, DARE, and CINAHL). Search terms (webappendix p 1)

See Online for webappendix

For the **Medion database** see http://www.mediondatabase.nl

included MeSH terms and free text: "serious infections", "children", "clinical and laboratory tests", and "ambulatory care". No time or language restrictions were placed on these searches. The first search was undertaken in October, 2008, with an update undertaken in June, 2009. We checked reference lists of all retrieved articles and relevant guidelines from the National Institute for Health and Clinical Excellence published before 2008.[11,12] The Medion database was checked for systematic reviews by use of the "signs and symptoms" subheading. Additionally, domain experts (European Research Network on Recognising Serious Infection investigators) were asked to review the list of studies identified and to report any obvious omissions.

Selection was done by two independent reviewers (AVdB and TH-H), after piloting on a sample of 20 studies.

	Design	Setting; country	Number of children	Proportion of children with serious infection (%)	Quality rating	Age range	Inclusion criteria	Exclusion criteria
Serious infections, composite outcome								
Andreola et al (2007)[21]	Prosp, cx, consec	ED; Italy	408	23·0%	C	<3 years	Fever of uncertain source and increased risk of SBI—ie, all infants aged 7 days to 3 months with rectal temperature >38°C and children aged 3–36 months with ill/toxic appearance or with rectal temperature >39·5°C	Antibiotics or vaccination in 48 h before enrolment, known immunodeficiencies, any chronic pathology, fever >5 days
Baker et al (1990)[22]	Prosp, consec	ED; USA	126	29·4%	C	26–56 days	Temperature (rectal) >38·2°C	NR
Berger et al (1996)[23]	Prosp, cx, consec	ED; Netherlands	138	23·9%	B	2 weeks to 1 year	Temperature (rectal) ≥38·0°C measured on the ward	Gestational age <37 weeks; perinatal complications; antibiotics or vaccination in previous 48 h; known previous or underlying disease
Bleeker et al (2007)[24]	Prosp, cx, consec	ED; Netherlands	381	26·0%	D	1–36 months	Referred to ED for fever without source—ie, temperature ≥38°C for which no clear focus could be identified after assessment by the GP or after history taking by paediatrician	Not referred by GP; immune deficiencies
Galetto-Lacour et al (2001)[25]	Prosp, cx	ED; Switzerland	124	22·6%	D	7 days to 36 months	Temperature (rectal) >38·0°C and no localising signs of infection from history or physical examination	Fever >7 days, neonates <1 week of age, children treated with ABs during the preceding 2 days, children with known immunodeficiencies
Galetto-Lacour et al (2003)[26]	Prosp, cx	ED; Switzerland	99	29·3%	D	7 days to 36 months	Temperature (rectal) >38°C and without localising signs of infection in their history or at physical examination	Fever >7 days, neonates <1 week of age, children treated with ABs during the preceding 2 days, children with known immunodeficiencies
Grupo de Trabajo (2001)[27]	Prosp, cx, consec	ED; Spain	739	19·9%	D	0–36 months	Temperature (rectal) ≥38°C	ABs or DTP within 48 h or MMR within 10 days; systemic central nervous condition; concomitant analytical changes in blood that interfere with interpretation of CBC; fever duration >72 h; chronic illness
Hsiao et al (2006)[28]	Prosp, cx, consec	ED; USA	429	10·3%	C	57–180 days	Temperature (rectal) >37·9°C	NR
McCarthy et al (1987)[29]	Prosp, cx, consec	ED; USA	143	19·6%	C	<24 months	Temperature ≥38·3°C	NR
McCarthy et al (1982)[30]	Prosp, cx, consec	ED; USA	165	15·8%	C	<24 months	Temperature ≥38·3°C	NR
Nademi et al (2001)[31]	Prosp, cx, consec	PAU; UK	141	29·1%	D	0–16 years	Temperature ≥38°C	Temperature <38°C
Thayyil et al (2005)[32]	Prosp, cx, consec	PD; UK	72	11·1%	D	1–36 months	Temperature >39°C without localising signs of infection	ABs 72 h before enrolment, immunodeficiencies, fever >7 days
Thompson et al (2009)[33]	Prosp, cx, consec	PAU; UK	700	55·3%	C	3 months to 16 years	Suspicion of acute infection	Children with diseases liable to cause repeated serious bacterial infection and infections resulting from penetrating trauma
Trautner et al (2006)[34]	Prosp, cx	ED; USA	103	19·4%	C	<17 years	Temperature (rectal) ≥41·1°C	None
Van den Bruel et al (2007)[5]	Prosp, cx, consec	GP, APC, ED; Belgium	3981	0·78%	C	<17 years	Acute illness for a maximum of 5 days	Traumatic or neurological illness, intoxication, psychiatric or behavioural problems without somatic cause, exacerbation of a chronic condition

(Continues on next page)

	Design	Setting; country	Number of children	Proportion of children with serious infection (%)	Quality rating	Age range	Inclusion criteria	Exclusion criteria
(Continued from previous page)								
Bacteraemia								
Crocker et al (1985)[35]	Prosp, cx, consec	ED; USA	201	10·5%	C	6 months to 2 years	Temperature (rectal) ≥39·4°C	Viral exanthema, enanthema, croup, vomiting, diarrhoea, admitted with a diagnosis of meningitis or sepsis
Haddon et al (1999)[36]	Prosp, cx	ED; Australia	526	3·4%	C	3–36 months	Temperature (tympanic) ≥39°C	Varicella, croup, or herpes gingivostomatitis
Jaffe et al (1991)[37]	Prosp, cx	ED; Canada	955	2·8%	C	3–36 months	Temperature (rectal) ≥39·0°C	Focal infection needing immediate AB; clinical appearance necessitating immediate hospital admission; specific viral infections; known immunodeficiency condition or chronic illness; AB or DTP within preceding 48 h
Osman et al (2002)[38]	Prosp, consec	ED; UK	1547	2·5%	D	0–14 years	All children with an infectious illness	NR
Teele et al (1975)[39]	Prosp, cx, consec	ED; USA	600	3·2%	C	4 weeks to 2 years	Temperature (rectal) ≥38·3°C	Previous medical assessment or referral from other clinician or from other clinic
Waskerwitz et al (1981)[40]	Prosp, cx, consec	ED; USA	292	5·8%	B	<24 months	Temperature (rectal) ≥39·5°C	Not previously healthy; weight less than third percentile or known chronic disease
Gastroenteritis causing dehydration								
Gorelick et al (1997)[41]	Prosp, cx	ED; USA	186	33·4%	C	1 month to 5 years	Chief complaint of vomiting, diarrhoea, or poor oral fluid intake	Symptoms >5 days; history of cardiac or renal disease or diabetes; malnutrition or failure to thrive: treatment within 12 h in other health facility; hyponatraemia or hypernatraemia; tonsillectomy within 10 days; no telephone or beeper for follow-up
Shavit et al (2006)[42]	Prosp	ED; Canada	83	15·7%	C	1 month to 5 years	History of diarrhoea (with or without vomiting) for ≤5 days and who were judged by the ED triage nurse to have some degree of dehydration	History of cardiovascular or renal disease; judged by the triage nurse to need emergent medical intervention
Meningitis								
Joffe et al (1983)[43]	Retro	ED; USA	241	5·4%	D	6 months to 6 years	First episode of fever and seizures	Did not undergo lumbar puncture and final outcome was not available; children with a predisposition to meningitis
Offringa et al (1992)[44]	Retro, Consec	ED; Netherlands	309	7·4%	C	3 months to 6 years	First episode of fever and seizures	NR
Oostenbrink et al (2001)[45]	Retro	ED; Netherlands	256	38·7%	C	1 month to 15 years	Signs of meningeal irritation	Patients with a history of severe neurological disease or ventricular drainage, and those referred from other hospitals
Pneumonia								
Mahabee-Gittens et al (2005)[46]	Prosp, cx	ED; USA	510	8·6%	A	2–59 months	Cough and at least one of laboured, rapid, or noisy breathing, chest or abdominal pain, or fever	Currently taking ABs, smoke inhalation, foreign body aspiration, or chest trauma; known diagnoses of asthma, bronchiolitis, sickle cell disease, cystic fibrosis, chronic cardiopulmonary disease
Taylor et al (1995)[47]	Prosp, cx, consec	ED; USA	572	7·3%	D	<2 years	Temperature ≥38·0°C	Acute wheezing or stridor, history of chronic pulmonary disease, chest radiograph interpreted as indeterminate by both radiologists (n=2), clinical diagnosis of pneumonia with no radiograph obtained (n=2)
Meningococcal infection								
Nielsen et al (2001)[48]	Prosp, cx, consec	PD; Denmark	208	18·8%	C	>1 month to <16 years	Haemorrhages in the skin, detected at admission or during hospital stay plus rectal temperature >38°C within 24 h of admission	Second or more inclusion in the study
Wells et al (2001)[49]	Prosp, cx, consec	ED; UK	218	11·0%	C	≤15 years	Non-blanching rash	NR

Prosp=prospective. Cx=cross-sectional. Consec=consecutive. Retro=retrospective. ED=emergency department. SBI=serious bacterial infection. NR=not reported. GP=general practitioner. ABs=antibiotics. DTP=diphtheria, tetanus, and pertussis vaccine. MMR=measles, mumps, and rubella vaccine. CBC=complete blood count. PAU=paediatric assessment unit. PD=paediatric department. GP=general practice. APC=ambulatory paediatric care. See text for definitions of quality rating.

Table 1: **Characteristics of included studies**

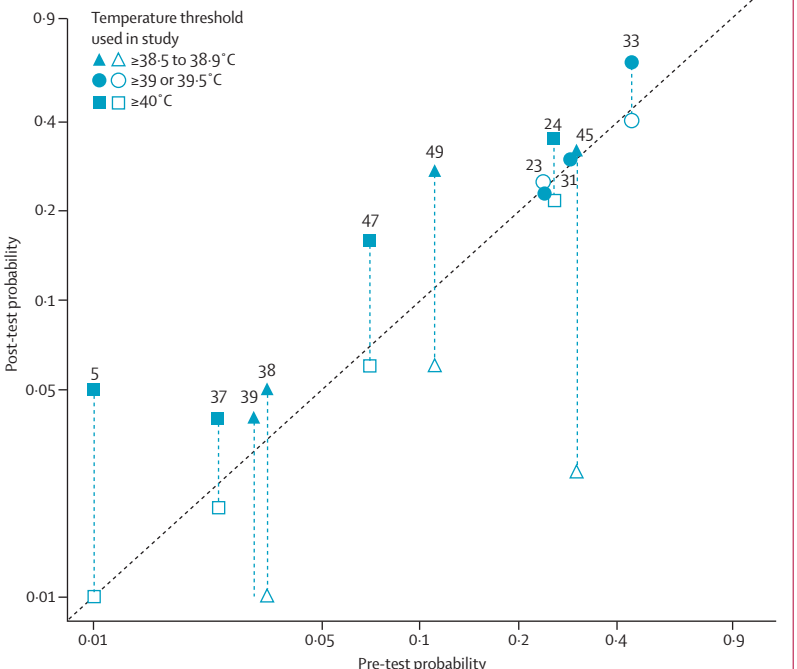

***Figure 2*: Probability of serious illness in children, by temperature threshold**
Reference numbers of studies are shown. Temperature above (closed symbols) or below (open symbols) threshold in eight studies in health-care settings with different pre-test probabilities of serious infection. The distance of the symbol from the diagonal line indicates the diagnostic value of temperature measurement in the study (applying the specified threshold). The height above the diagonal line gives the rule-in value; the height below the line the rule-out value. The figure is plotted on a log scale to achieve visual separation of the studies done in settings with a low prevalence of infection (in reference 45, the estimated post-test probability was 0% if the temperature was below 38·5°C, which cannot be plotted on a log scale, so there is no lower symbol). For studies that reported more than one cutoff point, only the value with the highest positive likelihood ratio is shown; for example, the study in a low prevalence setting also reported cutoff points of ≥38°C (positive likelihood ratio 1·50 and negative likelihood ratio 0·40) and ≥39°C (positive likelihood ratio 2·30 and negative likelihood ratio 0·60).[5] Two of the studies in high prevalence settings also reported data for temperature cutoff points of ≥38·5°C, 39·0°C, and 40·0°C, all of which were associated with likelihood ratios of approximately 1·00.[24,31]

Discrepancies between the reviewers were resolved by a third independent reviewer (MT).

The studies were selected in two rounds, first on title and abstract and second on full text, against the six criteria shown in the panel.

Quality assessment

Quality of selected studies and assessment of potential bias was assessed by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) instrument, including additional items as recommended by the Cochrane Collaboration.[13] Quality assessment was completed by one reviewer (AVdB) and checked by a second reviewer (TH-H). Any disagreements were resolved by discussion involving all researchers when appropriate. In cases where doubt remained, study investigators were contacted for clarification. The first two QUADAS items (spectrum bias and reference standard validity) were used as exclusion criteria. Spectrum bias was judged present in case-control studies with healthy controls, or in studies in which participants were selected on the basis of the performance of the reference standard. The validity of the reference standard was judged by a clinical review committee consisting of a minimum of three researchers.

Studies selected for analysis were given an A, B, C, or D rating. If insufficient data were given to be confident that a criterion had been met, it was assessed as not being met. Studies fulfilling all QUADAS criteria were rated A. Studies without total verification with the reference standard or with interpretation of the index feature unblinded to the results of the reference standard were rated D. Studies without an independent reference standard, with interpretation of the reference standard unblinded to the results of the index feature, or with an unduly long period between recording of the index feature and outcome were rated C. All other studies were rated B.

Data extraction and analysis

Data were extracted by one reviewer (AVdB) and checked by a second reviewer (TH-H). Any identified errors were discussed and corrected; two-by-two tables were reconstructed on the basis of information in the study or information retrieved from the study investigators. In the case of an empty cell, 0·5 was added to each cell. We calculated the likelihood ratios for the presence (positive likelihood ratio) or absence (negative likelihood ratio) of each clinical feature and pre-test and post-test probabilities of the outcome. Confidence intervals were calculated on the basis of the standard error of a proportion by use of STATA version 9.2. The post-test values for temperature were plotted against pre-test prevalence on a log scale by use of R software. All other clinical features were categorised on the basis of their diagnostic value as either red flags (ie, warning signs for serious infection) or as rule-out signs for serious infection. Clinical features were deemed red flags if, when positive, they substantially raised the probability of illness—ie, positive likelihood ratio of more than 5·0. Clinical features were deemed rule-out signs if, when negative, they substantially lowered the probability of illness—ie, negative likelihood ratio of less than 0·2.[14] When a study reported more than one result on the same clinical feature with different cut-off points, the result with the highest positive likelihood ratio or lowest negative likelihood ratio was reported. Features were included in the figures if at least one study reported a positive likelihood ratio of more than 5·0 or negative likelihood ratio of less than 0·2.

We categorised studies according to setting, with prevalence of serious infection as a proxy: less than 5% was defined as low prevalence, 5–20% as intermediate, and more than 20% as high prevalence setting. We report both the pre-test and post-test probabilities of serious infection for each study in dumbbell plots. Meta-analysis was done with the bivariate method in STATA version 9.2 when at least four studies on that clinical feature were available.

	Study reference	Prevalence*	Age range	Likelihood ratio (95% CI)	
				Positive	Negative
Global assessment					
Parental concern†	5	Low	<17 years	14·40 (9·30–22·10)	0·55 (0·39–0·78)
Clinician instinct that something wrong	5	Low	<17 years	23·50 (16·80–32·70)	0·38 (0·24–0·60)
Clinical impression	5	Low	<17 years	8·30 (6·25–11·10)	0·37 (0·23–0·62)
	36	Intermediate	3–36 months	1·05 (0·15–7·48)	1·00 (0·90–1·11)
	40	Intermediate	<24 months	2·75 (1·56–4·86)	0·64 (0·41–1·00)
	49‡	Intermediate	≤15 years	4·27 (2·98–6·11)	0·26 (0·12–0·56)
	42§	Intermediate	1 month to 5 years	4·14 (2·33–7·35)	0·28 (0·10–0·77)
Child appears ill	27	Intermediate	0–36 months	2·20 (1·78–2·78)	0·65 (0·55–0·77)
	24	High	1–36 months	1·40 (1·15–1·71)	0·67 (0·50–0·88)
Child behaviour					
Changed crying pattern	5	Low	<17 years	10·50 (4·62–13·20)	0·67 (0·51–0·89)
	24	High	1–36 months	0·74 (0·56–0·96)	1·30 (1·07–1·60)
	45‡	High	1 month to 15 years	0·49 (0·25–0·96)	1·16 (1·03–1·31)
Child drowsy	5	Low	<17 years	6·60 (4·17–10·50)	0·65 (0·49–0·86)
	44¶	Intermediate	3 months to 6 years	1·99 (1·29–3·08)	0·65 (0·42–1·00)
	45¶	High	1 month to 15 years	2·43 (1·82–3·26)	0·37 (0·25–0·56)
Child moaning	5	Low	<17 years	5·90 (1·97–17·70)	0·92 (0·81–1·03)
Child inconsolable	5	Low	<17 years	5·50 (2·66–11·50)	0·83 (0·69–0·99)

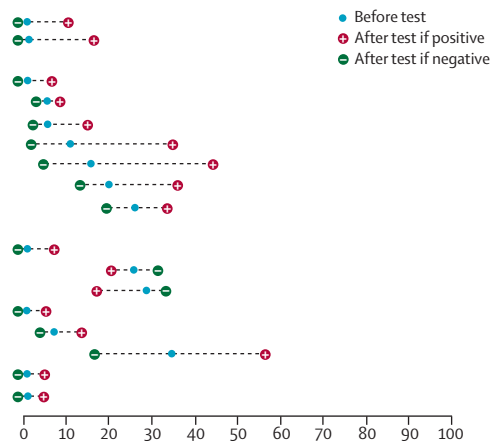

***Figure 3*: Potential warning signs for serious illness (positive likelihood ratio >5·0 in at least one study)—global assessment and behavioural features**
*Setting: low prevalence of serious infection (<5%); intermediate prevalence of serious infection (5–20%); high prevalence of serious infection (>20%). †Parental concern that the illness is different from previous illness. ‡Meningococcal infection only. §Gastroenteritis causing dehydration only. ¶Meningitis only.

	Study reference	Prevalence*	Age range	Likelihood ratio (95% CI)	
				Positive	Negative
Cyanosis	5	Low	<17 years	52·20 (10·50–258)	0·93 (0·85–1·03)
	33	High	3 months to 16 years	2·66 (1·73–4·10)	0·87 (0·82–0·93)
	45†	High	1 month to 15 years	50·20 (2·97–846)	0·88 (0·81–0·95)
Poor peripheral circulation	5‡	Low	<17 years	38·80 (11·20–134)	0·90 (0·80–1·02)
	42§	Intermediate	1 month to 5 years	4·71 (2·07–10·7)	0·52 (0·29–0·94)
	42§¶	Intermediate	1 month to 5 years	10·50 (5·00–22·1)	0·04 (0·03–0·60)
	33	High	3 months to 16 years	17·70 (2·36–132)	0·92 (0·88–0·96)
	41‡§	High	1 month to 5 years	11·70 (4·78–28·7)	0·55 (0·43–0·69)
	45†	High	1 month to 15 years	3·71 (2·32–5·93)	0·56 (0·44–0·73)
	24	High	1–36 months	2·39 (1·50–3·82)	0·83 (0·73–0·94)
Crackles	5	Low	<17 years	6·00 (3·52–10·10)	0·72 (0·56–0·91)
	46‖	Intermediate	2–59 months	1·51 (0·81–2·83)	0·92 (0·79–1·07)
Decreased breathing sounds	5	Low	<17 years	9·30 (4·42–19·70)	0·82 (0·68–0·98)
	46‖	Intermediate	2–59 months	2·21 (0·89–5·50)	0·93 (0·84–1·04)
Short of breath	5	Low	<17 years	9·30 (5·83–14·80)	0·64 (0·48–0·85)
	46‖	Intermediate	2–59 months	1·11 (0·70–1·74)	0·96 (0·78–1·18)
	24	High	1–36 months	3·60 (2·06–6·28)	0·81 (0·72–0·91)
Rapid breathing	5	Low	<17 years	9·78 (5·71–16·70)	0·70 (0·55–0·89)
	47‖	Intermediate	<2 years	3·08 (2·41–3·94)	0·37 (0·23–0·60)
	33	High	3 months to 16 years	1·26 (1·07–1·49)	0·80 (0·68–0·94)

***Figure 4*: Potential warning signs for serious illness (positive likelihood ratio >5·0 in at least one study)—circulatory and respiratory features**
*Setting: low prevalence of serious infection (<5%); intermediate prevalence of serious infection (5–20%); high prevalence of serious infection (>20%). †Meningitis only. ‡Capillary refill more than 2 s. §Gastroenteritis causing dehydration only. ¶Digitally measured capillary refill. ‖Pneumonia only.

Role of the funding source
The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit the paper for publication. All authors had full access to all the data in the study. The corresponding author had final responsibility for the decision to submit for publication.

Results
Figure 1 shows the flow diagram of study selection for the analysis. We selected 36 studies for final inclusion in the review, six of which focused on laboratory tests only and are not included in the analysis reported here.[15–20] Full details of the remaining 30 studies are shown in table 1.

The quality of the included studies was modest (webappendix p 2). Only four studies explicitly mentioned

	Study reference	Prevalence*	Age range	Likelihood ratio (95% CI)	
				Positive	Negative
Meningeal irritation	5	Low	<17 years	25·70 (3·09–213)	0·97 (0·91–1·03)
	44†	Intermediate	3 months to 6 years	275 (16·70–4526)	0·52 (0·35–0·76)
	48‡	Intermediate	>1 month to 16 years	13·90 (5·41–35·60)	0·61 (0·47–0·79)
	45†	High	1 month to 15 years	2·57 (2·16–3·06)	0·01 (0·00–0·15)
Petechial rash	5	Low	<17 years	12·50 (1·65–94·9)	0·97 (0·91–1·03)
	44†	Intermediate	3 months to 6 years	83·70 (4·50–1475)	0·86 (0·73–1·01)
	48‡§	Intermediate	>1 month to 6 years	9·00 (5·26–15·3)	0·28 (0·16–0·48)
	49‡§	Intermediate	≤15 years	7·00 (4·60–10·70)	0·19 (0·08–0·46)
	45†	High	1 month to 15 years	6·18 (2·68–14·30)	0·81 (0·73–0·91)
	32	Intermediate	1–36 months	8·90 (2·63–30·40)	0·75 (0·63–0·91)
Seizures	5	Low	<17 years	20·70 (4·83–88·60)	0·94 (0·86–1·03)
	43†¶	Intermediate	6 months to 6 years	5·90 (1·79–19·00)	0·80 (0·59–1·08)
	44†¶	Intermediate	3 months to 6 years	3·50 (1·69–7·17)	0·76 (0·58–1·00)
	45†	High	1 month to 15 years	1·68 (0·66–4·27)	0·96 (0·90–1·04)
Unconsciousness	5	Low	<17 years	19·80 (6·17–63·50)	0·91 (0·81–1·02)
	44†	Intermediate	3 months to 6 years	155 (9·03–2677)	0·73 (0·57–0·93)
Decreased skin elasticity	41‖	High	1 month to 5 years	10·70 (3·87–29·8)	0·67 (0·56–0·81)
Hypotension**	49‡	Intermediate	≤15 years	9·40 (1·99–44·70)	0·74 (0·56–0·99)
Any abnormal finding in history or physical examination	29	Intermediate	<24 months	4·42 (2·87–6·80)	0·18 (0·71–0·44)

***Figure 5*: Potential warning signs for serious illness (positive likelihood ratio >5·0 in at least one study)—miscellaneous**

*Setting: low prevalence of serious infection (<5%); intermediate prevalence of serious infection (5–20%); high prevalence of serious infection (>20%). †Meningitis only. ‡Meningococcal infection. §Diameter more than 2 mm. ¶During examination. ‖Gastroenteritis causing dehydration only. **Hypotension defined as 2 SD or more below the mean for age.

masked reading of the reference standard; this item was scored as unclear in 18 studies. Only seven studies reported indeterminate or intermediate results. Most studies were undertaken in emergency departments, with four studies done in paediatric departments (two paediatric assessment units),[31–33,48] and only one done in general practice (which also recruited non-referred patients from ambulatory paediatric care and the emergency department).[5] Median prevalence of serious infection was 15·4% (IQR 8·0–23·2). 15 studies used a composite outcome of serious infections consisting of sepsis, bacteraemia, meningitis, pneumonia, and urinary tract infection (and in some cases additional infections such as cellulitis, osteomyelitis, and abscess). A further six studies reported specifically on bacteraemia, three on meningitis, and two each on pneumonia, meningococcal infection, and gastroenteritis causing dehydration (table 1).

Figure 2 shows the value of temperature measurement for diagnosis of serious infection, with different cut-off points and in settings with different prevalences of serious infection. The highest rule-in value was obtained in the setting with the lowest prevalence, where a temperature of 40°C or more increased the likelihood of disease from 0·8% to 5·0%.[5] By contrast, the absence of high temperature (<38·5°C to 38·9°C) had greatest rule-out value in a study with prevalence of serious infection of 29·1%.[31] However, this rule-out potential was not seen in any of the other five studies with prevalence more than 20% and temperature had no rule-in value in these high prevalence studies.

Figures 3–5 show potential red flags for serious infection (ie, features with a positive likelihood ratio of more than 5·0 in at least one study). Both parental concern that the illness is different from previous illnesses (positive likelihood ratio 14·40) and the clinician's instinct that something is wrong (positive likelihood ratio 23·50) are important red flags in a setting with a low prevalence of serious infection (figure 3). The strongest red flags for circulatory or respiratory impairment are cyanosis, rapid breathing, shortness of breath, and markers of poor peripheral circulation (figure 4). Changed crying pattern was a potential red flag in a low prevalence setting but paradoxically reduced the probability of serious disease in a high prevalence setting. Meningeal irritation, petechial rash, and unconsciousness are important red flags in all settings (figure 5).

Figure 6 reports clinical decision rules with the potential to exclude the possibility of serious infection. The most widely studied rule, the Yale Observation Scale, did not provide satisfactory results. Although the negative likelihood ratio in two studies was less than 0·2,[30,32] in five other studies it ranged from 0·68 to 0·97,[21,22,25,26,28] and was associated with post-test probabilities ranging from 10% to 28%. The study in which this score was originally described obtained data in 1980–81, before immunisation against *Haemophilus influenzae* and pneumococcus, possibly accounting for its better performance.[30] However, this explanation would not account for the similar results of the second study,[32] which was done in 2003 in a similar population of patients to the five other studies.

Meta-analysis of the seven Yale Observation Scale studies was limited by significant heterogeneity (p=0·002), which remained (p=0·026) after exclusion of the first study with a negative likelihood ratio of less than 0·2,[30] but disappeared (p=0·093) after exclusion of both studies.[32] The summary sensitivity of the five remaining

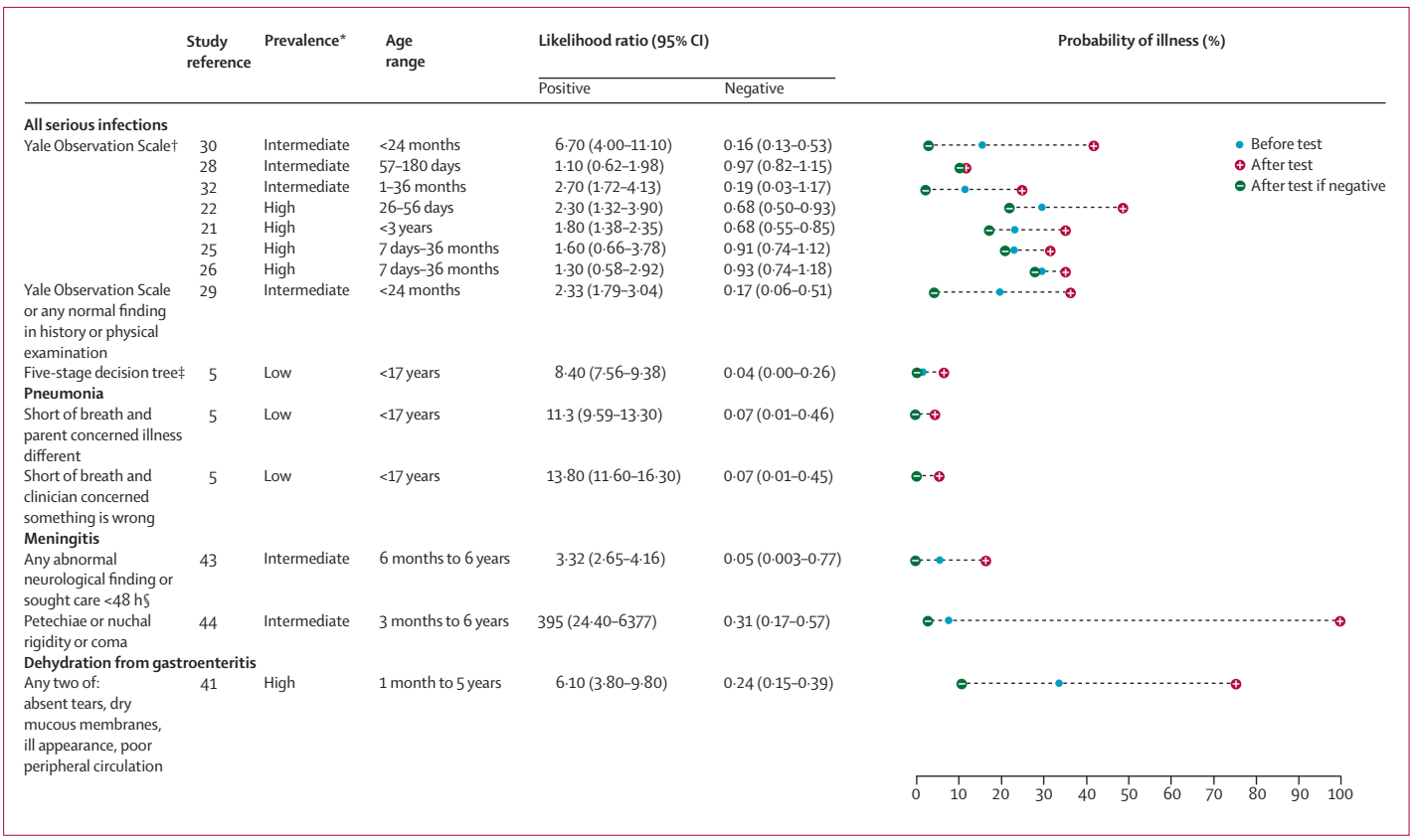

***Figure 6*: Clinical decision rules with the potential to rule in or rule out serious infection (positive likelihood ratio >5·0 or negative likelihood ratio <0·2 in at least one study)**
*Setting: low prevalence of serious infection (<5%); intermediate prevalence of serious infection (5–20%); high prevalence of serious infection (>20%). †Cutoff point used: reference 34, more than 8; reference 21, more than 9; references 24, 27, 28, 30 and 32, more than 10. ‡If yes to any of five sequential questions: (1) clinician instinct that something is wrong, (2) dyspnoea, (3) temperature more than 39·5°C, (4) diarrhoea, (5) age 15–29 months. §Sought care within 48 h before seizure.

studies was 32·5% (95% CI 21·7–45·5), with a specificity of 78·9% (95% CI 73·9–83·1), theoretically corresponding to a positive likelihood ratio of 2·90 and negative likelihood ratio of 0·86.

The best clinical decision rule for excluding the possibility of serious infection (negative likelihood ratio 0·04), based on one study,[5] involved a five-stage decision tree (figure 6). The rule decreased the probability of serious infections to 0·03% if negative, but classified 10% of children as potentially seriously ill if positive. The two decision rules for excluding the possibility of pneumonia (absence of breathlessness combined with absence of either parent or clinician concern) performed equally well (negative likelihood ratio 0·07, post-test probability <0·01%).

Table 2 shows clinical features that were less helpful in either confirming or excluding the possibility of serious infection. Common signs and symptoms (cough, headache, tummy ache, vomiting, diarrhoea, poor feeding, signs of upper respiratory tract infection) have little diagnostic value. Failure to smile (positive likelihood ratio 4·24) and changed breathing pattern (positive likelihood ratio 4·43) are just below the arbitrary cutoff point of 5·0, so might have some value in confirming but not in excluding (negative likelihood ratio 0·64 and 0·67, respectively) the possibility of serious infection. The presence of a reactive child (moving, reaching for objects, looking around the room)[23] or one who is not irritable[31] have little diagnostic value in high prevalence settings. Abnormal skin colour, described variably as cyanotic, pallor, or flushed or mottled, seems to be unhelpful as a descriptor, despite the fact that cyanosis and poor peripheral perfusion (which causes mottling and pallor) are red flags (figure 4).

In studies of specific infections, the less helpful clinical features (table 3) in most cases replicate the findings in table 2. Respiratory rate was the most reliable clinical sign in the diagnosis of pneumonia (positive likelihood ratio 2·70–4·00 depending on cutoff point) but breathlessness and auscultatory signs (decreased breath sounds, crackles, wheezing) had less diagnostic value for pneumonia than for serious infection as a composite outcome (figure 4).[5,46,47] The individual signs of dehydration from gastroenteritis (low urine output, sunken eyes, dry mucous membranes, tachycardia, abnormal respiration) were all associated with modest likelihood ratios (positive likelihood ratio 1·82–3·71).

	Prevalence*	Likelihood ratio	
		Positive	Negative
Global assessement			
No obvious source of fever[28]	Intermediate	3·04	0·87
Decision rule†[24]	High	2·07	0·38
NICE traffic light system‡[33]	High	1·20	0·50
Manchester triage system[33]	High	1·35	0·43
Decision rule§[33]	High	1·31	0·52
Child behaviour			
Child no longer smiles[5]	Low	4·24	0·64
Child is irritable[5,31]	Low and high	1·33–2·34	0·57–0·86
Child is somnolent[5]	Low	2·25	0·81
Child is reactive¶[23]	High	1·33–1·97	0·56–0·79
Respiratory signs			
Changed breathing pattern[5]	Low	4·43	0·67
Cough[5]	Low	1·30	0·73
Signs of URTI[5,34]	Low and intermediate	0·46–0·99	1·01–2·21
Gastrointestinal signs			
Diarrhoea[5,23,34]	Low, intermediate, and high	0·99–2·91	0·69–1·00
Vomiting[5,24,31,34]	Low, intermediate, and high	0·83–1·60	0·69–1·10
Signs of dehydration‖[5,24]	Low and high	1·07–2·49	0·98
Poor feeding[5,31]	Low and high	1·37–1·54	0·51–0·83
Other signs and symptoms			
Age[23,28,34]	Intermediate and high	0·98–2·49	0·77–1·01
Underlying condition[34]	Intermediate	2·42	0·76
Duration of fever or illness[5,21,23,24,34]	Low, intermediate, and high	0·76–2·18	0·74–1·53
Abnormal skin colour[5,23,24]	Low and high	1·59–1·95	0·61–0·97
Tummy ache[5]	Low	0·41	1·15
Headache[5]	Low	0·23	1·20
Tachycardia**[33]	High	1·49–2·05	0·65–0·85

Clinical features were deemed warning signs if, when positive, they substantially raised the probability of illness—ie, positive likelihood ratio of more than 5·0. Clinical features were deemed rule-out signs if, when negative, they substantially lowered the probability of illness—ie, negative likelihood ratio of less than 0·2. NICE=National Institute for Health and Clinical Excellence. URTI=upper respiratory tract infection. *Setting: low prevalence of serious infection (<5%); intermediate prevalence of serious infection (5–20%); high prevalence of serious infection (>20%). †Duration of fever (days), history of vomiting, ill clinical appearance, chest wall retractions with or without rapid breathing, poor peripheral circulation. ‡One red or amber feature or more. §At least one of the following: temperature 39°C or more, oxygen saturation 94% or less, tachycardia, rapid breathing. ¶Moving limbs, reaching for objects, looking around the room; in isolation or in combination. ‖Other than skin inelasticity. **Advanced Pediatric Life Support age-specific cut-off points or heart rate more than 90th centile.

Table 2: **Clinical features of limited help in confirming or excluding the possibility of any serious infection**

Discussion

The strongest red flags for serious infection identified in this systematic review accord with those previously identified by WHO for resource-poor countries: reduced consciousness, convulsions, cyanosis, rapid breathing, and slow capillary refill (table 4).[9] Parental concern and clinician global impression were also identified as important diagnostic features in developed countries. Difficulty in feeding seems to be a less helpful red flag in developed countries than it is in developing countries. Temperature of more than 40°C has value as a red flag in settings with a low prevalence of serious infection. No single clinical feature has rule-out value but some simple combinations can be used to exclude the possibility of serious infection—for example, pneumonia is very unlikely if the child is not short of breath and there is no parental concern.

The main strength of this systematic review is that it highlights the nature and difficulty of the diagnostic task facing primary care and hospital clinicians responsible for identifying seriously ill children at initial presentation in countries where serious childhood illness is now rare. We systematically reviewed a range of publications from which less than 2% of potentially relevant studies provided adequate and relevant data for inclusion. We devised innovative methods to aggregate and present the data so that the results make sense to clinicians, with graphical representation of the change in the pre-test and post-test likelihood of serious illness associated with each clinical feature.

The main weaknesses of our report stem from the limitations of the studies identified. The most obvious limitation is the paucity of studies from first-contact care settings. One potential weakness that is common to all diagnostic studies assessing symptoms and clinical signs is reproducibility. The diagnostic value of a symptom varies depending on whether it is spontaneously reported or elicited by questioning. The inter-observer agreement between clinicians on clinical signs such as capillary refill time is often poor. Additionally, cultural and language differences make aggregation of data from different countries difficult.

A major contrast of our results with the Integrated Management of Childhood Illness recommendations[50] is that diagnosis of serious infection in children in developed countries is extremely challenging. Even warning signs associated with a likelihood ratio of 5–10 (for example, temperature ≥40°C) might not raise the probability of disease above 5% in a primary care setting. Referring all children with a 5% risk to hospital would overwhelm hospital services; however, informed parents would probably be unhappy to know that their child was not being referred despite a 1 in 20 risk of serious infection. Our analysis also highlights the difficulty of excluding the possibility of serious infection on the basis of individual clinical features—clinicians in developed countries might think that this is the most important finding. Our report shows that infection can only be ruled out if several clinical features are considered together. However, the best known clinical decision rule, the Yale Observation Scale, proved disappointing in ruling out serious infection.

We excluded some studies that have contributed substantially to the study of diagnosis of serious illness in children. Baby Check is a score devised to help parents and clinicians to detect all serious illness (not simply infection, hence its exclusion) in children aged less than 6 months.[51] In a series of 87 children from UK general practice (of whom three had serious infection), the score had a sensitivity of 100% and a specificity of 67% (positive likelihood ratio 3·0) at the recommended cutoff score of

	Prevalence*	Likelihood ratio	
		Postive	Negative
Bacteraemia			
Child is irritable[35]	Intermediate	1·48	0·61
Child is lethargic[35]	Intermediate	0·64	1·10
Functional status†[40]	Intermediate	1·21–2·57	0·26–0·55
Age (various cut-offs)[39]	Low	0·33–1·83	0·66–1·13
Referral status[36]	Low	1·74	0·79
Meningitis			
Child is irritable[45]	High	0·76	1·05
Vomiting[44]	Intermediate	2·53	0·64
Duration of fever or illness[44]	Intermediate	1·43	0·81
Sought care in previous 48 h[43,44]	Intermediate	2·28–2·92	0·64–0·73
Paresis or paralysis[44]	Intermediate	3·48	0·76
Meningococcal infection			
Cough[48]	Intermediate	0·41	1·35
Vomiting[48]	Intermediate	1·08	0·94
Pneumonia			
Grunting[46]	Intermediate	0·56	1·02
Wheezing[46]	Intermediate	1·25	0·95
Duration[46]	Intermediate	1·03	0·93
Dehydration from gastroenteritis			
Abnormal respiration[41]	High	3·10	0·66
Tachycardia[41]	High	2·18	0·68
Abnormal radial pulse[41]	High	3·10	0·66
Sunken eyes[41]	High	3·71	0·47
Dry mucous membranes[41]	High	3·62	0·26
Low urine output[41]	High	1·82	0·27

Clinical features were deemed warning signs if, when positive, they substantially raised the probability of illness—ie, positive likelihood ratio of more than 5·0. Clinical features were deemed rule-out signs if, when negative, they substantially lowered the probability of illness—ie, negative likelihood ratio of less than 0·2. *Setting: low prevalence of serious infection (<5%); intermediate prevalence of serious infection (5–20%); high prevalence of serious infection (>20%). †With or without clinician impression of bacteraemia.

Table 3: **Clinical features of limited help in confirming or excluding possibility of specific infections**

	WHO Young Infants Study (2008)[9]* (odds ratio [95% CI])	Studies in this review† (range of odds ratios)
History and behaviour		
Convulsions	15 (6–37)	5–22
Difficulty in feeding	10 (7–15)	2–3
Reduced consciousness	7 (3–16)	22–212
Lethargy	4 (2–7)	3
Stiff limbs	15 (2–106)	NR
Hypothermia‡	9 (5–19)	NR
Circulation and respiration		
Cyanosis	14 (16–117)	56
Slow capillary refill	11 (5–22)	9–262
Rapid breathing	3 (2–4)	8–14
Severe chest wall retraction	9 (4–21)	NR
Grunting	3 (1–8)	2

*The WHO Young Infants Study[9] included 3177 children aged less than 2 months recruited from Bangladesh, Bolivia, Ghana, India, Pakistan, and South Africa; the odds ratios reported are for children less than 6 days old although the researchers say that the same clinical predictors can be used for children 7–59 days old with similar operating characteristics. †For better comparison, the range reported includes only studies in settings with low and intermediate prevalence. ‡Temperature less than 35·5°C).

Table 4: **Comparison of predictors of serious illness identified by this analysis of studies in developed countries with those identified by the WHO Young Infants Study in developing countries**

less than 8; if used to predict all children needing hospital admission, sensitivity fell to 80% but with no change in specificity (positive likelihood ratio 2·4).[51] A key study on diagnosis of dehydration in children was similarly excluded from our analysis because it included children who had been admitted to hospital.[52] In the diagnosis of 5% or more dehydration, Mackenzie and colleagues[52] reported a positive likelihood ratio of 1·5 for decreased skin elasticity and 2·5 for decreased peripheral perfusion.

Many of the included studies had only a moderate QUADAS quality rating. However, several of these deficits are difficult to avoid in this particular clinical situation. For example, identical verification of all children for a composite outcome of serious infections is not feasible, because it would require procedures such as lumbar puncture, chest radiograph, and blood tests in every child. Moreover, clinical features are part of the definition of sepsis, by which the reference standard cannot be interpreted in a masked manner from the index test.

There were few studies from settings with a low prevalence of serious infection and there was often substantial heterogeneity between studies. In many cases, the heterogeneity was explicable in terms of setting, inclusion criteria, and cutoff values used. Additionally, some studies obtained data before the introduction of vaccines against *H influenzae* or pneumococcus. The interpretation of the data for temperature is especially difficult because in some studies high temperature was a criterion for inclusion. However, we do not think that the exclusion of apyrexial children from several studies in high prevalence settings is sufficient to account for the poor performance of temperature overall in such settings. Finally, although we excluded studies that focused on neonates, our analysis included studies that spanned a wide age range. This weakness is attenuated by the fact that several studies created dichotomous predictive variables (eg, rapid breathing) by applying age-specific cutoff values. However, very few studies reported results by age; to disaggregate age, it would be necessary to undertake an individual patient data meta-analysis, which we will attempt in the future.

The study that provided evidence for the importance of parental concern and instinct of the clinician was done in primary care with a prevalence of serious infection of

only 0·78%.[5] Although we would like to see the importance of parental concern and clinician instinct replicated in other studies, these results are unlikely to be chance effects—the study was large (N=3981) and the importance of findings from clinical global assessment was also seen in other studies. The finding is also consistent with the fact that the clinical features that alarm parents and clinicians in their overall assessment (eg, changes in a child's behaviour, changed crying pattern, and inconsolability) were also identified as red flags in other studies in developed countries.

Not only do red flags have less diagnostic value in developed countries than developing countries, they will also be seen infrequently even in children with serious infection. For example, parental concern that the illness was different was noted in only 3·4% of children and in around half the cases of serious infection (46·4%) the parent did not express such concern.[5] Similarly, clinicians reported poor peripheral circulation in 0·3% of children but it was a sign at presentation in only 10% of serious cases. This finding emphasises that identification of red flags is not enough. Children with serious illness who do not have red flags at presentation will be missed if effective safeguards are not put in place.[53]

Many of the clinical features that did not reach our predefined threshold individually could nonetheless provide useful information for clinical practice when considered in combination—for example, dry mucous membranes for the diagnosis of dehydration (positive likelihood ratio 4·1)[41] or diarrhoea for the composite outcome of serious infection.[5,34] The most effective clinical decision rule identified was based on following up two red flags (clinician's instinct that something is wrong and dyspnoea) by asking three further questions about borderline red flags:[5] temperature, diarrhoea, and age. But, as the example of the Yale Observation Scale shows, combining several borderline red flags, such as child not smiling, reactivity, and skin colour, does not necessarily produce a useful decision rule, since the Yale score gives equal and categorical weight to every item. Additionally, skin colour is a combination of features, including pallor and mottled skin, which could be of variable importance and subject to variation in interpretation between clinicians.

Most of the red flags already recommended by WHO for use in developing countries can be used in the initial assessment of children presenting to ambulatory care settings in developed countries. There should be more emphasis on parental concern in the diagnostic process. However, we now need to identify the level of risk at which clinical action should be taken. Additionally, the relative inability of any combination of clinical features to effectively exclude the possibility of serious illness in a one-off consultation means that parents need to be more actively involved in monitoring red flags and taking precautionary measures.

Contributors

AVdB conceived the study, undertook the literature search and analyses, and drafted the report. TH-H undertook the literature search and analyses, and co-drafted the report. MT conceived the study, undertook the literature search and analyses, and commented on the report. FB conceived the study and commented on the report. DM conceived the study, undertook the analyses, and co-drafted the report.

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Conflicts of interests

We declare that we have no conflicts of interest.

References

1 CEMACH. Why children die: a pilot study 2006; England (South West, North East and West Midlands), Wales and Northern Ireland. London: CEMACH, 2008.

2 Bruijnzeels MA, Foets M, van der Wouden JC, van den Heuvel WJ, Prins A. Everyday symptoms in childhood: occurrence and general practitioner consultation rates. *Br J Gen Pract* 1998; **48:** 880–84.

3 Fleming DM, Smith GE, Charlton JR, Charlton J, Nicoll A. Impact of infections on primary care—greater than expected. *Commun Dis Public Health* 2002; **5:** 7–12.

4 Armon K, Stephenson T, Gabriel V, et al. Determining the common medical presenting problems to an accident and emergency department. *Arch Dis Child* 2001; **84:** 390–92.

5 Van den Bruel A, Aertgeerts B, Bruyninckx R, Aerts M, Buntinx F. Signs and symptoms for diagnosis of serious infections in children: a prospective study in primary care. *Br J Gen Pract* 2007; **57:** 538–46.

6 Kai J. What worries parents when their preschool children are acutely ill, and why: a qualitative study. *BMJ* 1996; **313:** 983–86.

7 Riordan FA, Thomson AP, Sills JA, Hart CA. Who spots the spots? Diagnosis and treatment of early meningococcal disease in children. *BMJ* 1996; **313:** 1255–56.

8 Thompson MJ, Ninis N, Perera R, et al. Clinical recognition of meningococcal disease in children and adolescents. *Lancet* 2006; **367:** 397–403.

9 The Young Infants Clinical Signs Study Group. Clinical signs that predict severe illness in children under age 2 months: a multicentre study. *Lancet* 2008; **371:** 135–42.

10 Duke T, Oa O, Mokela D, Oswyn G, Hwaihwanje I, Hawap J. The management of sick young infants at primary health centres in a rural developing country. *Arch Dis Child* 2005; **90:** 200–05.

11 NICE. Feverish illness in children: assessment and initial management in children younger than 5 years. London: National Institute for Health and Clinical Excellence, 2007.

12 NICE. Urinary tract infection in children: diagnosis, treatment and long-term management. London: National Institute for Health and Clinical Excellence, 2007.

13 Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol* 2003; **3:** 25.

14 Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. *JAMA* 1994; **271:** 703–07.

15 Bachur RG, Harper MB. Predictive model for serious bacterial infections among infants younger than 3 months of age. *Pediatrics* 2001; **108:** 311–16.

16 Bonadio WA, Hagen E, Rucka J, Shallow K, Stommel P, Smith D. Efficacy of a protocol to distinguish risk of serious bacterial infection in the outpatient evaluation of febrile young infants. *Clin Pediatr (Phila)* 1993; **32:** 401–04.

17 Lacour AG, Zamora SA, Gervaix A. A score identifying serious bacterial infections in children with fever without source. *Pediatr Infect Dis J* 2008; **27:** 654–56.

18 Garra G, Cunningham SJ, Crain EF. Reappraisal of criteria used to predict serious bacterial illness in febrile infants less than 8 weeks of age. *Acad Emerg Med* 2005; **12:** 921–25.

19 Baker MD, Bell LM, Avner JR. Outpatient management without antibiotics of fever in selected infants. *N Engl J Med* 1993; **329:** 1437–41.

20 Baker MD, Bell LM, Avner JR. The efficacy of routine outpatient management without antibiotics of fever in selected infants. *Pediatrics* 1999; **103:** 627–31.

21 Andreola B, Bressan S, Callegaro S, Liverani A, Plebani M, Da Dalt L. Procalcitonin and C-reactive protein as diagnostic markers of severe bacterial infections in febrile infants and children in the emergency department. *Pediatr Infect Dis J* 2007; **26:** 672–77.

22 Baker MD, Avner JR, Bell LM. Failure of infant observation scales in detecting serious illness in febrile, 4- to 8-week-old infants. *Pediatrics* 1990; **85:** 1040–43.

23 Berger RM, Berger MY, van Steensel-Moll HA, Dzoljic-Danilovic G, Derksen-Lubsen G. A predictive model to estimate the risk of serious bacterial infections in febrile infants. *Eur J Pediatr* 1996; **155:** 468–73.

24 Bleeker SE, Derksen-Lubsen G, Grobbee DE, Donders AR, Moons KG, Moll HA. Validating and updating a prediction rule for serious bacterial infection in patients with fever without source. *Acta Paediatr* 2007; **96:** 100–04.

25 Galetto-Lacour A, Gervaix A, Zamora SA, et al. Procalcitonin, IL-6, IL-8, IL-1 receptor antagonist and C-reactive protein as identificators of serious bacterial infections in children with fever without localising signs. *Eur J Pediatr* 2001; **160:** 95–100.

26 Galetto-Lacour A, Zamora SA, Gervaix A. Bedside procalcitonin and C-reactive protein tests in children with fever without localizing signs of infection seen in a referral center. *Pediatrics* 2003; **112:** 1054–60.

27 Grupo de Trabajo sobre el Nino Febril de la Sociedad Espanola de Urgencias de P. The young febrile child. Results of a multicenter survey. *An Esp Pediatr* 2001; **55:** 5–10 (in Spanish).

28 Hsiao AL, Chen L, Baker MD. Incidence and predictors of serious bacterial infections among 57- to 180-day-old infants. *Pediatrics* 2006; **117:** 1695–701.

29 McCarthy PL, Lembo RM, Fink HD, Baron MA, Cicchetti DV. Observation, history, and physical examination in diagnosis of serious illnesses in febrile children less than or equal to 24 months. *J Pediatr* 1987; **110:** 26–30.

30 McCarthy PL, Sharpe MR, Spiesel SZ, et al. Observation scales to identify serious illness in febrile children. *Pediatrics* 1982; **70:** 802–09.

31 Nademi Z, Clark J, Richards CG, Walshaw D, Cant AJ. The causes of fever in children attending hospital in the north of England. *J Infect* 2001; **43:** 221–25.

32 Thayyil S, Shenoy M, Hamaluba M, Gupta A, Frater J, Verber IG. Is procalcitonin useful in early diagnosis of serious bacterial infections in children? *Acta Paediatr* 2005; **94:** 155–58.

33 Thompson MJ, Coad N, Harnden A, Mayon-White R, Perera R, Mant D. How well do vital signs identify children with serious infections in paediatric emergency care? *Arch Dis Child* 2009; **94:** 888–93.

34 Trautner BW, Caviness AC, Gerlacher GR, Demmler G, Macias CG. Prospective evaluation of the risk of serious bacterial infection in children who present to the emergency department with hyperpyrexia (temperature of 106 degrees F or higher). *Pediatrics* 2006; **118:** 34–40.

35 Crocker PJ, Quick G, McCombs W. Occult bacteremia in the emergency department: diagnostic criteria for the young febrile child. *Ann Emerg Med* 1985; **14:** 1172–77.

36 Haddon RA, Barnett PL, Grimwood K, Hogg GG. Bacteraemia in febrile children presenting to a paediatric emergency department. *Med J Aust* 1999; **170:** 475–78.

37 Jaffe DM, Fleisher GR. Temperature and total white blood cell count as indicators of bacteremia. *Pediatrics* 1991; **87:** 670–74.

38 Osman O, Brown D, Beattie T, Midgley P. Management of febrile children in a paediatric emergency department. *Health Bull (Edinb)* 2002; **60:** 33–39.

39 Teele DW, Pelton SI, Grant MJ, et al. Bacteremia in febrile children under 2 years of age: results of cultures of blood of 600 consecutive febrile children seen in a "walk-in" clinic. *J Pediatr* 1975; **87:** 227–30.

40 Waskerwitz S, Berkelhamer JE. Outpatient bacteremia: clinical findings in children under two years with initial temperatures of 39·5 degrees C or higher. *J Pediatr* 1981; **99:** 231–33.

41 Gorelick MH, Shaw KN, Murphy KO. Validity and reliability of clinical signs in the diagnosis of dehydration in children. *Pediatrics* 1997; **99:** E6.

42 Shavit I, Brant R, Nijssen-Jordan C, Galbraith R, Johnson DW. A novel imaging technique to measure capillary-refill time: improving diagnostic accuracy for dehydration in young children with gastroenteritis. *Pediatrics* 2006; **118:** 2402–08.

43 Joffe A, McCormick M, DeAngelis C. Which children with febrile seizures need lumbar puncture? A decision analysis approach. *Am J Dis Child* 1983; **137:** 1153–56.

44 Offringa M, Beishuizen A, Derksen-Lubsen G, Lubsen J. Seizures and fever: can we rule out meningitis on clinical grounds alone? *Clin Pediatr (Phila)* 1992; **31:** 514–22.

45 Oostenbrink R, Moons KG, Donders AR, Grobbee DE, Moll HA. Prediction of bacterial meningitis in children with meningeal signs: reduction of lumbar punctures. *Acta Paediatr* 2001; **90:** 611–17.

46 Mahabee-Gittens EM, Grupp-Phelan J, Brody AS, et al. Identifying children with pneumonia in the emergency department. *Clin Pediatr (Phila)* 2005; **44:** 427–35.

47 Taylor JA, Del Beccaro M, Done S, Winters W. Establishing clinically relevant standards for tachypnea in febrile children younger than 2 years. *Arch Pediatr Adolesc Med* 1995; **149:** 283–87.

48 Nielsen HE, Andersen EA, Andersen J, et al. Diagnostic assessment of haemorrhagic rash and fever. *Arch Dis Child* 2001; **85:** 160–05.

49 Wells LC, Smith JC, Weston VC, Collier J, Rutter N. The child with a non-blanching rash: how likely is meningococcal disease? *Arch Dis Child* 2001; **85:** 218–22.

50 Gove S. Integrated management of childhood illness by outpatient health workers: technical basis and overview. The WHO Working Group on guidelines for Integrated Management of the Sick Child. *Bull World Health Organ* 1977; **75** (suppl 1): 7–24.

51 Morley CJ, Thornton AJ, Green SJ, Cole TJ. Field trials of the Baby Check score card in general practice. *Arch Dis Child* 1991; **66:** 111–14.

52 Mackenzie A, Barnes G, Shann F. Clinical signs of dehydration in children. *Lancet* 1989; **334:** 605–07.

53 Almond S, Mant D, Thompson M. Diagnostic safety-netting. *Br J Gen Pract* 2009; **59:** 872–74.