The Kern Fever in the Emergency Department Study (Kern FEDS): Clinical appearance, serious bacterial illness, and the meaning of uncertainty.

Background: Emergency department (ED) fever management algorithms require the clinician to categorize febrile children as 'ill' or 'not ill' appearing when determining the risk for serious bacterial illness (SBI). This study describes a natural experiment where an ED pediatric chart allowed clinicians a third option, 'unsure'. **Hypotheses**: We hypothesized (1) that chart prompts would improve documentation of clinical appearance, and (2) that exam findings and prevalence of serious bacterial illness in infants categorized as 'unsure' would be intermediate between those who were ill and not ill appearing. **Design**: We conducted a retrospective study of 3005 ED patients aged 0-24 months who had microbiology testing for fever in the ED between 1/1/2006 and 11/30/2009. We modeled overall appearance as the dependent and individual physical findings as the independent variables with ordinal logistic regression to help establish the validity of clinical appearance as a concept. We then compared the prevalence of the components of SBI, bacterial meningitis, pneumonia, urinary tract infection (UTI) and positive blood cultures, between the categorizations, not ill appearing, unsure and ill appearing. **Results**: Clinical appearance was documented in 60/583 (10.3%) whose encounter was recorded on the template without prompts versus 2036/2420 (84%) with prompts ($p<0.001$). Age odds ratio (OR) 1.04 (95% CI 1.01, 1.07) weight (quintile) OR 0.81 (95% CI 0.70, 0.95), dehydration OR 9.68 (95% CI 7.17, 13.01), tachycardia OR 1.31 (95% CI 1.04, 1.68), tachypnea OR 2.44 (95% CI 1.61, 3.68), prior antipyretics OR 0.65 (95% CI 0.52, 0.83) and prior antibiotics OR 2.56 (95%CI 1.71, 3.82) were associated with appearance. There was an ordinal relationship between appearance and the prevalence of bacterial meningitis and pneumonia for the categories ill appearing, unsure, and not ill appearing. The prevalence of positive blood cultures among children categorized as 'not ill appearing' and 'unsure' was similar. Urinary tract infection (UTI) prevalence was similar regardless of appearance.

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Conclusion: Charting prompts increased documentation of clinical appearance. There was an ordinal relationship between the prevalence of meningitis, and pneumonia, across the categories 'ill appearing', 'unsure' and 'not ill appearing'. This was not the case for blood cultures or UTI.

Title

The Kern Fever in the Emergency Department Study: Clinical appearance, serious bacterial illness, and the meaning of uncertainty.

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Abbreviations

ED Emergency Department

SBI Serious bacterial illness

LIS Laboratory information system

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ABSTRACT

Background

Emergency department (ED) fever management algorithms require the clinician to categorize febrile children as 'ill' or 'not ill' appearing when determining the risk for serious bacterial illness (SBI). This study describes a natural experiment where an ED pediatric chart allowed clinicians a third option, 'unsure'.

Hypotheses

We hypothesized (1) that chart prompts would improve documentation of clinical appearance, and (2) that exam findings and prevalence of serious bacterial illness in infants categorized as 'unsure' would be intermediate between those who were ill and not ill appearing.

Design

We conducted a retrospective study of 3005 ED patients aged 0-24 months who had microbiology testing for fever in the ED between 1/1/2006 and 11/30/2009. We modeled overall appearance as the dependent and individual physical findings as the independent variables with ordinal logistic regression to help establish the validity of clinical appearance as a concept. We then compared the prevalence of the components of SBI, bacterial meningitis, pneumonia, urinary tract infection (UTI) and positive blood cultures, between the categorizations, not ill appearing, unsure and ill appearing.

Results

Clinical appearance was documented in 60/583 (10.3%) whose encounter was recorded on the template without prompts versus 2036/2420 (84%) with prompts ($p<0.001$). Age odds ratio (OR) 1.04 (95% CI 1.01, 1.07) weight (quintile) OR 0.81 (95% CI 0.70, 0.95), dehydration OR 9.68 (95% CI 7.17, 13.01), tachycardia OR 1.31 (95% CI 1.04, 1.68), tachypnea OR 2.44 (95% CI 1.61, 3.68), prior antipyretics OR 0.65 (95% CI 0.52, 0.83) and prior antibiotics OR 2.56 (95%CI 1.71, 3.82) were associated with appearance. There was an ordinal relationship between appearance and the prevalence of bacterial meningitis and pneumonia for the categories ill appearing, unsure, and not ill appearing. The prevalence of positive blood cultures among children categorized as 'not ill appearing' and 'unsure' was similar. Urinary tract infection (UTI) prevalence was similar regardless of appearance.

Conclusion

Charting prompts increased documentation of clinical appearance. There was an ordinal relationship between the prevalence of meningitis, and pneumonia, across the categories 'ill appearing', 'unsure' and 'not ill appearing'. This was not the case for blood cultures or UTI.

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INTRODUCTION

Most fever is viral in origin; but failing to diagnose serious bacterial illness (SBI) in infants and toddlers can lead to serious consequences including death. Serious bacterial illness includes bacterial meningitis, pneumonia, urinary tract infection (UTI) and bacteremia. The emergency department (ED) evaluation of the febrile infant or toddler is focused on determining whether or not the child has an SBI.

This evaluation begins with a clinical assessment of the child's appearance, and whether the child is ill appearing. This assessment of the child's overall appearance forms the basis for management guidelines and even influences the physician's assessment of other physical findings.(McCarthy et al. 1985) Experience suggests that overall appearance is a continuum. It is sometimes difficult to classify a child as 'ill' or 'not ill appearing' with any certainty. Current management algorithms admit no uncertainty and require the physician choose 'ill' or 'not ill' appearing. (Baker, M. Douglas, Bell & Avner 1993; Baraff et al. 1993; Baskin, O'Rourke & Fleisher 1992; Jaskiewicz et al. 1994)

Historically, three categories of overall appearance categories, namely 'ill,' 'questionably ill', and 'well appearing' have been used. The use of these terms was deprecated in the 1970s as subjective and vague.(McCarthy, Jekel & Dolan 1977) The Yale observation score (YOS) was an attempt to eliminate such subjectivity. The YOS weighted objective physical findings associated with SBI.(McCarthy et al. 1985; McCarthy et al. 1982) As the limitations of the YOS emerged, (Baker, M. D., Avner & Bell 1990; Van den Bruel et al. 2010) febrile infant algorithms derived specifically for emergency medicine reintroduced the concept of overall appearance. These algorithms did not reintroduce the 'questionably ill' classification but required the physician to choose (using varying terminologies) between two categories, 'ill' or 'not ill appearing.' (Baker, M. Douglas, Bell & Avner 1993; Baraff et al. 1993; Baskin, O'Rourke & Fleisher 1992; Jaskiewicz et al. 1994; Mintegi et al. 2014)

Current researchers diverge as to the importance of overall clinical appearance. Some have tried to objectify appearance with variables such as 'state variation' and 'grabbing for objects.'(Brent et al. 2011) Others have embraced overall appearance as useful. In one classification and regression tree analysis of 3,981 febrile children, a physician's sense that 'there is something wrong' was the single most important predictor of SBI. (Van den Bruel et al. 2007)

Overall clinical appearance must be associated with the presence of SBI to be useful. Overall clinical appearance is likely to be associated with at least some objective physical findings if it is a valid concept. Conversely, reducing overall clinical appearance to only some of its associated physical findings may discard subtle but meaningful information. Since clinical appearance is a continuum, there may also be value in physician uncertainty as to whether or not a child is ill appearing. We intuit this uncertainty would be associated with higher SBI prevalence and more objective physical findings than those of children who are 'ill' but lower prevalence and fewer findings than among those who are 'not ill' appearing.

In 2006 our ED switched from a generic paper template chart for all patients to a template designed for children younger than 24 months. When designing this template, we created three categories for overall appearance. These categories were 'ill appearing', 'unsure', and 'not ill appearing.' Here we describe this natural experiment in an ED which allowed us to observe how clinicians used these three categories; whether these categories were associated with objective physical findings; and to determine if there was an ordinal relationship between these three categories of appearance and the components of SBI.

We hypothesized that (1) this charting prompts would increase physician documentation of the overall appearance of infants and toddlers presenting with fever compared to the generic template; (2) objective physical exam findings would be associated with but not fully explain severity of illness classification; and (3) there would be an ordinal relationship between the prevalence of meningitis, positive blood cultures, urinary tract infections and pneumonia, across the categories 'ill appearing,' 'unsure' and 'not ill appearing.'

METHODS

Study design and setting

This was a retrospective study of children younger than 24 months seen in an ED between January 2006 and November 2009. The ED was in a public teaching hospital and was staffed by board-certified or eligible emergency physicians (EP), mid-level providers, and emergency medicine residents. During the study period the ED volume was 49,000 patients annually, of whom 23% were younger than 14 years old.

Identification of participants

We included subjects if they were evaluated in the ED for either parentally reported or confirmed (by ED measurement) fever, and had any of the following investigations performed: urinalysis, urine microscopy, urine culture, CSF analysis including gram stain culture and polymerase chain reaction testing if performed, or blood culture. Subjects were excluded if they were evaluated for fever but had none of these investigations performed. We identified potential subjects from the hospital laboratory information system (LIS). We extracted microbiology results from the LIS. All study subjects had at least one laboratory investigation performed.

Our LIS could not reliably distinguish outpatient clinic from outpatient ED visits. Research assistants (RA) in the first instance reviewed medical records of the list of potentially eligible subjects identified by the LIS and excluded those whose had not been seen in the ED.

Data abstraction

The medical record was completed by a physician or mid-level provider. Investigators and research assistants (RA) reviewed these scanned images of paper medical records using an explicit electronic template for data entry. RAs were trained using formal instruction, practice sessions, and one-on-one individual training by a physician investigator. In addition to initial training, intermittent instruction and reminders were provided as needed. As a safeguard, 20% of all charts abstracted by RAs were reviewed by a physician investigator. Physician investigators abstracted 50% of the charts. Regular meetings addressed data abstraction and interpretation issues. The clinical information abstracted from medical records is listed in **Appendix 1**. Because we could not blind all the abstractors to our hypotheses, those investigators who abstracted medical records did not manage the microbiology results.

We did not impute missing data. We did not measure inter-rater reliability of our primary independent variable as this was either explicitly documented or missing. Similarly our microbiological outcomes were objectively defined. Difficulties in the interpretation of recorded physical findings (mostly difficulties in the interpretation of handwriting) were addressed by either AC or PW as they arose.

Study definitions and outcomes

We defined culture proven UTI as more than 10,000 colony forming units (cfu) of a recognized pathogen in a catheterized specimen. (Sharp 2009; Wilson & Gaido 2004) We defined a probable UTI as urinalysis positive for nitrites or both bacteruria and more than 10 white blood cells (WBC) per high-powered field (hpf).(Sharp 2009) We defined a possible UTI as the presence of either bacteruria or >10 WBC per hpf. (Sharp 2009) We defined positive blood cultures as growth of a single known pathogen. In the case of organisms which could be either a contaminant or a pathogen, such as *Streptococcus viridans*, we deferred to the clinical diagnosis. We defined bacterial meningitis as growth of any bacteria in the cerebrospinal fluid (CSF) or a positive Gram stain. We accepted a clinical diagnosis of meningitis in the absence of CSF growth if there was CSF pleocytosis, low CSF glucose, or elevated CSF protein and the remainder of the clinical course was consistent with the diagnosis. We included herpes simplex encephalitis and bacterial meningitis as one group for analysis because they both are life threatening, have similar presentations, and require LP for diagnosis We defined viral meningitis as CSF pleocytosis abnormal for age but with less than 1000 WBC per hpf, normal glucose and protein, and negative gram stain and culture and negative CSF and blood cultures(Tunkel et al. 2004). When the diagnosis of SBI was uncertain, we deferred to the discharge diagnosis. Discharge diagnoses were taken from the ED record for patients sent home from the ED and the hospital discharge summary for admitted patients. We based the diagnosis of pneumonia on the clinicians' diagnosis. We did not attempt to distinguish viral from bacterial pneumonia.

We defined fever as a rectal temperature at triage ≥38°C, tachycardia as heart rate (HR) greater than 150 and tachypnea as respiratory rate ≥70 for neonates, ≥60 for infants, and ≥55 children aged 12-24 months. We chose this as one definition for tachycardia because HR >150 appears to be a widely used heuristic by many EPs and impressions of overall clinical appearance are typically formed quickly and rely on such heuristics. We also used a definition of tachycardia as HR ≥98th centile for age.(Siberry, Iannone & Childs 2000) Other clinical factors, such as dehydration, were based on the clinicians' documentation.

Analysis

We described our hypotheses graphically, performed univariate analysis using Fisher's exact test and ordinal logistic regression (OLR) for ordered dependent variables. We performed subgroup analyses for those older and younger than three months of age by introducing the variable age less than three months in ordinal regression. Correction for multiple testing was performed for each component of our SBI outcomes. (Holland & Copenhaver 1988; Newson 2010) We further examined the effect of age, weight and clinical findings on reported appearance using OLR. We performed OLR across the categories ill appearing, unsure, and not ill appearing. For OLR models we performed a likelihood-ratio test of whether the coefficients were equal across categories and a Brant test to verify the proportional odds ratio assumption inherent in this technique.(Brant 1990; Long 1997) We checked for outliers and influential observations using graphical techniques on two maximum likelihood logistic regression models alternately including the 'unsure' with the 'ill' and 'not ill' appearing groups.

Data management and statistical analysis were performed using Stata 13 (Statacorp LLP, College Station, TX). The Kern Medical Center institutional review board approved this study and granted a waiver of consent (approval # 09011).

RESULTS AND DISCUSSION

Results

We identified 5,857 children younger than 24 months from 86,827 LIS records. After initial chart review we identified 3,005 as eligible ED patients; of these 1,498 (50%) were male. The patients are described in **Table 1**. Clinical appearance was documented in 60/583 (10%) children whose encounter was recorded using the generic template and in 2036/2420 (84%) of children whose encounter was recorded using the pediatric template (Fishers exact $p<0.001$). Apart from template use, those in whom clinical appearance was not documented were broadly similar to those in whom it was. Two encounters were documented solely by dictation; overall appearance was recorded in one of these. Urinalyses were obtained in 2,437 (81%) patients, urine cultures in 1,587 (53%), blood cultures in 1,669 (56%), and CSF analyses and cultures in 376 (13%). Overall clinical appearance was documented in 2,098/3005 (70%). The category 'unsure' was the least frequently used 264/2,098 (13%); 324/2,098 (15%) were considered 'ill', and 1510/2098 (72%) 'not ill' appearing. **Figure 1** shows the intensity of microbiological testing, urine, blood and CSF testing by clinical appearance.

Clinical factors associated with more concerning clinical appearance in multivariate OLR are shown in **Table 2**. Physicians' classification of infants and toddlers as 'ill appearing,' 'unsure' and 'not ill appearing' was associated with age, weight, dehydration, tachypnea, HR >150 bpm, home administration of antipyretics and prior antibiotics. The proportional odds assumption required for OLR was met. Tachycardia defined as HR≥98th centile for age was not statistically significant (p=0.07) but had a similar coefficient to tachycardia defined as HR>150 bpm (**Appendix 2.)** Duration of illness was not associated with either clinical appearance or prevalence of SBI; this may reflect our inclusion criterion of microbiological testing being obtained. The prevalence of the diagnoses encountered is shown in **Figure 2**.

Figures 3 shows the outcomes for meningitis, positive blood cultures and UTI. There was an ordinal relationship between appearance and the outcomes of bacterial meningitis (p<0.009) and pneumonia (p<0.009) (both adjusted for multiple comparisons). The prevalence of positive blood cultures was similar among children who were considered 'not ill appearing' (2%) and those categorized as 'unsure' (1%). Blood cultures were positive in 4% of 'ill appearing' children p=0.025, p=0.183 adjusted for multiple comparisons). There was no association between clinical appearance and culture-proven UTI (p=0.088) or probable UTI (p=0.25) in both the total sample and (after adjusting for multiple comparisons) among only those who had urine tested.

In subgroup analysis of infants less than three months of age only the association between bacterial meningitis and clinical appearance remained statistically significant (p<0.001). These subgroup analyses are shown in **Figure 4**. Our findings also confirm what experienced clinicians have observed; rarely (1:750 in our data) a well appearing febrile infant harbors bacterial meningitis.

Discussion

Charting prompts increased documentation of the overall clinical appearance of febrile children younger than 24 months, but did not necessarily affect clinical care. Although ours was a retrospective study, and as such should be considered primarily a tool for developing hypotheses worthy of prospective testing, this finding was so strong and has such face validity that we recommend a check box or similar prompt to document overall clinical appearance should be part of ED charting templates for febrile infants.

We found that the classifications 'ill appearing,' 'unsure' and 'not ill appearing' were associated in an ordinal fashion with age, weight, prior antibiotic or antipyretic use and some physical exam findings. This finding should reassure practicing clinicians and those developing fever management guidelines that clinical appearance is indeed a valid concept.

As hypothesized, we found an ordinal relationship between the prevalence of bacterial meningitis, and to lesser extent pneumonia across the categories 'ill appearing,' 'unsure' and 'not ill appearing.' We could not reject the null hypothesis for bacteremia or UTI. The prevalence of positive blood cultures in the 'unsure' category mirrored those of the 'not ill appearing' category.

In febrile infants younger than three months, culturing for infection is routine. (Anon 2013; Baker, M. D., Avner & Bell 1990; Baskin, O'Rourke & Fleisher 1992) Some have found little or no association between SBI and clinical appearance, age or other clinical variables. (Hsiao, Chen & Baker 2006) Most studies do find similar associations to those we found, particularly in older children. (Nijman et al. 2013)A large study of children up to 5 years of age analyzed four categories of general appearance, (well, mildly unwell, moderately and very unwell appearing), in a multinomial (unordered) fashion and found that each was associated with a greater prevalence of bacterial infection (although the study excluded meningitis). (Craig, Jonathan C. et al. 2010) These authors did not include a 'unsure' category.(Craig, Jonathan C et al. 2010)

The lack of association we found between clinical appearance and UTI has also been observed elsewhere. (De et al. 2013; Newman et al. 2002; Zorc et al. 2005) Overall clinical appearance influences pediatricians' ordering of urine cultures but is not associated with UTI. (Newman et al. 2002)This lack of association between clinical appearance and UTI is reflected in current NICE guidelines for the management of febrile children. (Anon 2013)Our study reinforces these guidelines; the decision to test a febrile child's urine must not be based simply on overall appearance. With caveats for UTI and children less than three months of age, a physician's intuition that a child has a serious underlying infection is enough to warrant investigation.(Van den Bruel et al. 2012) The more certain the physician is that a child is ill appearing the greater the prevalance of SBI.

Current AAP guidelines recommend a 50,000 cfu threshold for diagnosing UTI. (Subcommittee On Urinary Tract, Steering Committee On Quality & Management 2011) This is based on a study that reported single organism growth in 8/23 and mixed growth in 15/23 of their urine specimens with colony counts in the range 10,000-49,000*[sic]* cfu. (Hoberman et al. 1994)

It is unclear to us that such an approach to diagnosing UTI is more useful than a threshold of 10,000 cfu growth of a single known pathogen. Algorithms for interpreting multiple pathogens in urine cultures are available.(Wilson & Gaido 2004)

There are limitations to our work. In many cases physicians did not provide any assessment of clinical appearance. Our study may therefore underestimate physician uncertainty. Given this inherent bias to the null in our study, and the similar findings of studies, future management algorithm developers should prospectively address the continuum of clinical appearance, recognize uncertainty, and move away from the false dichotomy on which current practice hinges.

We included only children who had testing performed. This constitutes a restricted sample of febrile children. This is evidenced by the observation that bronchiolitis appeared more common in ill-appearing than febrile children who did not appear ill. Only a minority of infants with bronchiolitis is febrile; SBI is very uncommon in bronchiolitis; and consequently only a minority of infants with bronchiolitis will need testing for SBI. (Chee et al. 2010)

Many infants and toddlers with fever do not have any testing performed, particularly in this era of pneumococcal vaccination. (Simon, Lukacs & Mendola 2011) These patients are not characterized by this study. This selection bias at once decreases the generalizability of our findings, yet reflects clinical practice. A related limitation is work up bias; not all children had all studies; for example only 13% had a LP. However even a prospective design could not mandate invasive procedures such as LP for all febrile infants and toddlers.

Our gold standards are imperfect. Blood cultures are insensitive. We accepted the clinical diagnosis in cases where blood cultures grew *Strep viridans* which is known to be pathogenic in some instances and not in others; this did not alter the results. In the case of pneumonia, where we relied on clinical diagnosis, there is a risk that clinicians would make the diagnosis in an ill but not a well appearing child with similar clinical findings. We minimized this risk by first demonstrating that overall appearance was associated with objective clinical findings. We are aware of one death from missed meningitis in the study period; however that infant had no testing performed and therefore was not included in this study. Because of the poor outcomes for untreated bacterial meningitis we think it unlikely that the diagnosis was missed among our study patients. We cannot be so sure for bacteremia or UTI.

Since management is determined in large part on the clinical appearance of the child we expect that classification of appearance was made on initial assessment of the patient. However because this was a retrospective study using a paper chart physicians could have restated their initial classification of appearance based on subsequent laboratory results. This could decrease the frequency with which clinical appearance may have been documented as 'unsure' and would bias our results against even the existence of uncertainty. The fact that physical findings were ordinally associated with clinical appearance suggests that such re-statement of clinical appearance with the benefit of hindsight, occurred infrequently if at all.

We took pains to minimize the limitations inherent in retrospective research by using an explicit clinical template, explicit chart review, the use of electronic data transfer where possible, careful repeated training of our RAs, and aggressive quality control of data entry procedures. Nonetheless a prospective design would have been preferred.

Another concern is that the introduction of a pediatric template points to efforts to improve pediatric emergency care and a possible secular effect. We are less concerned about this. First, we included a period in our study when the generic template was in use. Second, it took 18 months to obtain hospital permission to implement the pediatric template, so it is likely that our efforts at pediatric emergency care improvement had already taken effect.

We could not ascertain inter-rater reliability among physicians for their classification of overall appearance. However, we have previously demonstrated adequate inter-rater reliability for the categories of appearance we used. (Walsh et al. 2014) Complexities that we have not addressed here are that early in the course of severe illnesses infants may look well, and that judgment of clinical appearance requires acumen and experience, both of which vary between clinicians.

The next paradigm shift in the management of febrile infants will likely be the adoption of technology capable of measuring infant's differing RNA transcription responses to viral and bacterial infection, and mass spectrometry based methods which directly detect urinary pathogens.(DeMarco & Burnham 2014; Ferreira et al. 2010; Scagnolari et al. 2009) These may supersede traditional culturing. Judicious use of such novel technologies may usefully include stratification based in part on overall appearance, including a category for when the physician is unsure. Language optimization matters, and terms such as 'neither ill nor well appearing' or 'questionably ill appearing' might have been more acceptable to users than 'unsure'. One physician commented that she was quite certain that she could not classify a particular infant as either 'ill' nor 'not ill' appearing but believed that the designation 'unsure' unfairly implied incompetence. Language optimization would address such issues. Parents seek certitude but the intellectual honesty of occasional uncertainty, at least among physicians, would allow for more informed risk stratification of febrile infants and toddlers.

CONCLUSION

Charting prompts increased documentation of clinical appearance in children being evaluated for fever. There was an ordinal relationship between the prevalence of meningitis, and pneumonia, across the categories 'ill appearing', 'unsure' and 'not ill appearing'. Bacteremia was similar in infants categorized as 'not ill appearing' or 'unsure.' There was no relationship between clinical appearance and the prevalence of UTI.

References

Anon 2013, NICE clinical guideline 160: Feverish illness in children Assessment and initial management in children younger than 5 years, 160 edn, vol. 1, 1 vols., National Institute for Clinical Excellence Guidelines, National Institute for Clinical Excellence, Manchester, UK.

Baker, MD, Avner, JR & Bell, LM 1990, 'Failure of Infant Observation Scales in Detecting Illness in Ferbile, 4- to 8-Week-Old Infants', Pediatrics, vol. 85, no. 6, pp. 1040-3.

Baker, MD, Bell, LM & Avner, JR 1993, 'Outpatient Management without Antibiotics of Fever in Selected Infants', New England Journal of Medicine, vol. 329, no. 20, pp. 1437-41.

Baraff, LJ, Schriger, DL, Bass, JW, Fleisher, GR, Klein, JO, McCracken, GH & Powell, KR 1993, 'Practice Guideline for the Management of Infants and Children 0 to 36 Months of Age With Fever Without Source', Pediatrics, vol. 92, no. 1, pp. 1-12.

Baskin, MN, O'Rourke, EJ & Fleisher, GR 1992, 'Outpatient treatment of febrile infants 28 to 89 days of age with intramuscular administration of ceftriaxone', The Journal of pediatrics, vol. 120, no. 1, pp. 22-7.

Brant, R 1990, 'Assessing proportionality in the proportional odds model for ordinal logistic regression', Biometrics, vol. 46, no. 4, pp. 1171-8.

Brent, AJ, Lakhanpaul, M, Thompson, M, Collier, J, Ray, S, Ninis, N, Levin, M & MacFaul, R 2011, 'Risk score to stratify children with suspected serious bacterial infection: observational cohort study', Archives of Disease in Childhood, vol. 96, no. 4, pp. 361-7.

Chee, C, Walsh, P, Kuan, S, Cabangangan, J, Azimian, K, Dong, C, Tobias, J & Rothenberg, SJ 2010, 'Emergency Department Septic Screening in Respiratory Syncytial Virus (RSV) and Non-RSV Bronchiolitis', Western Journal of Emergency Medicine, vol. 11, no. 1, pp. 60-7.

Craig, JC, Williams, GJ, Jones, M, Codarini, M, Macaskill, P, Hayen, A, Irwig, L, Fitzgerald, DA, Isaacs, D & McCaskill, M 2010, 'The accuracy of clinical symptoms and signs for the diagnosis of serious bacterial infection in young febrile children: prospective cohort study of 15781 febrile illnesses', BMJ vol. 340, no. 7755, c.1540.

De, S, Gabrielle, JW, Hayen, A, Macaskill, P, McCaskill, M, Isaacs, D & Craig, JC 2013, 'Accuracy of the “traffic light” clinical decision rule for serious bacterial infections in young children with fever: a retrospective cohort study', BMJ, vol. 346, p.:f866.

DeMarco, ML & Burnham, C-AD 2014, 'Diafiltration MALDI-TOF Mass Spectrometry Method for Culture-Independent Detection and Identification of Pathogens Directly From Urine Specimens', American Journal of Clinical Pathology, vol. 141, no. 2, pp. 204-12.

Ferreira, L, Sánchez-Juanes, F, González-Ávila, M, Cembrero-Fuciños, D, Herrero-Hernández, A, González-Buitrago, JM & Muñoz-Bellido, JL 2010, 'Direct Identification of Urinary Tract Pathogens from Urine Samples by Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry', Journal of Clinical Microbiology, vol. 48, no. 6, pp. 2110-5.

Hoberman, A, Wald, ER, Reynolds, EA, Penchansky, L & Charron, M 1994, 'Pyuria and bacteriuria in urine specimens obtained by catheter from young children with fever', The Journal of Pediatrics, vol. 124, no. 4, pp. 513-9.

Holland, BS & Copenhaver, MD 1988, 'Improved Bonferroni-type multiple testing procedures', Psychological Bulletin, vol. 104, no. 1, p. 145-9.

Hsiao, AL, Chen, L & Baker, MD 2006, 'Incidence and Predictors of Serious Bacterial Infections Among 57- to 180-Day-Old Infants', Pediatrics, vol. 117, no. 5, pp. 1695-701.

Jaskiewicz, JA, McCarthy, CA, Richardson, AC, White, KC, Fisher, DJ, Powell, KR & Dagan, R 1994, 'Febrile infants at low risk for serious bacterial infection—an appraisal of the Rochester criteria and implications for management', Pediatrics, vol. 94, no. 3, pp. 390-6.

Long, JS 1997, Regression Models for Categorical and Limited Dependent Variables, Sage, Thousand Oaks, CA.

McCarthy, PL, Jekel, JF & Dolan, TF 1977, 'Temperature Greater Than or Equal to 40 C in Children Less Than 24 Months of Age: A Prospective Study', Pediatrics, vol. 59, no. 5, pp. 663-8.

McCarthy, PL, Lembo, RM, Baron, MA, Fink, HD & Cicchetti, DV 1985, 'Predictive Value of Abnormal Physical Examination Findings in Ill-Appearing and Well-Appearing Febrile Children', Pediatrics, vol. 76, no. 2, pp. 167-71.

McCarthy, PL, Sharpe, MR, Spiesel, SZ, Dolan, TF, Forsyth, BW, DeWitt, TG, Fink, HD, Baron, MA & Cicchetti, DV 1982, 'Observation Scales to Identify Serious Illness in Febrile Children', Pediatrics, vol. 70, no. 5, pp. 802-9.

Mintegi, S, Bressan, S, Gomez, B, Da Dalt, L, Blázquez, D, Olaciregui, I, de la Torre, M, Palacios, M, Berlese, P & Benito, J 2014, 'Accuracy of a sequential approach to identify young febrile infants at low risk for invasive bacterial infection', Emergency Medicine Journal, vol. 31, no. e1, pp. e19-e24.

Newman, T, Bernzweig, JA, Takayama, J, Finch, S, Wasserman, R & Pantell, R 2002, 'Urine testing and urinary tract infections in febrile infants seen in office settings: The pediatric research in office settings; febrile infant study', Archives of Pediatrics & Adolescent Medicine, vol. 156, no. 1, pp. 44-54.

Newson, RB 2010, 'Frequentist q-values for multiple-test procedures', Stata Journal, vol. 10, no. 4, pp. 568-84.

Nijman, RG, Vergouwe, Y, Thompson, M, van Veen, M, van Meurs, AH, van der Lei, J, Steyerberg, EW, Moll, HA & Oostenbrink, R 2013, 'Clinical prediction model to aid emergency doctors managing febrile children at risk of serious bacterial infections: diagnostic study', BMJ, vol. 346, p. f1706.

Scagnolari, C, Midulla, F, Pierangeli, A, Moretti, C, Bonci, E, Berardi, R, De Angelis, D, Selvaggi, C, Di Marco, P, Girardi, E & Antonelli, G 2009, 'Gene expression of nucleic acid-sensing pattern recognition receptors in children hospitalized for respiratory syncytial virus-associated acute bronchiolitis', Clinical and vaccine immunology : CVI, vol. 16, no. 6, pp. 816-23.

Sharp, SE (ed.) 2009, Cumitech 2C, Laboratory Diagnosis of Urinary Tract Infections., vol. 2C, 46 vols., Cumitech Cumulative techniques and procedures in clinical microbiology, American Society for Microbiology, Washington, DC.

Siberry, G, Iannone, R & Childs, B 2000, Harriet Lane Handbook: A manual for pediatric house officers., 15 edn, vol. 1, 1 vols., Mosby, St Louis.

Simon, AE, Lukacs, SL & Mendola, P 2011, 'Emergency Department Laboratory Evaluations of Fever Without Source in Children Aged 3 to 36 Months', Pediatrics, vol. 128, no. 6, pp. e1368-e75.

Subcommittee On Urinary Tract Infection, Steering Committee On Quality Improvement & Management 2011, 'Urinary Tract Infection: Clinical Practice Guideline for the Diagnosis and Management of the Initial UTI in Febrile Infants and Children 2 to 24 Months', Pediatrics 2011; vol 128, no. 3, pp. 595–610.

Tunkel, AR, Hartman, BJ, Kaplan, SL, Kaufman, BA, Roos, KL, Scheld, WM & Whitley, RJ 2004, 'Practice Guidelines for the Management of Bacterial Meningitis', Clinical Infectious Diseases, vol. 39, no. 9, pp. 1267-84.

Van den Bruel, A, Aertgeerts, B, Bruyninckx, R, Aerts, M & Buntinx, F 2007, 'Signs and symptoms for diagnosis of serious infections in children: a prospective study in primary care', The British Journal of General Practice, vol. 57, no. 540, p. 538-46.

Van den Bruel, A, Haj-Hassan, T, Thompson, M, Buntinx, F & Mant, D 2010, 'Diagnostic value of clinical features at presentation to identify serious infection in children in developed countries: a systematic review', The Lancet, vol. 375, no. 9717, pp. 834-45.

Van den Bruel, A, Matthew, T, Frank, B & David, M 2012, 'Clinicians' gut feeling about serious infections in children: observational study', BMJ, vol. 345, p. e6144.

Walsh, P, Thornton, JM, Walker, N, McCoy, JG, Baal, J, Baal, J, Mendoza, N, Banimahd, F & Asato, J 2014, 'Approaches to describing inter-rater reliability of the overall clinical appearance of febrile infants and toddlers in the Emergency Department', PeerJ PrePrints, vol. 2, p. e444v1.

Wilson, ML & Gaido, L 2004, 'Laboratory Diagnosis of Urinary Tract Infections in Adult Patients', Clinical Infectious Diseases, vol. 38, no. 8, pp. 1150-8.

Zorc, JJ, Levine, DA, Platt, SL, Dayan, PS, Macias, CG, Krief, W, Schor, J, Bank, D, Shaw, KN & Kuppermann, N 2005, 'Clinical and Demographic Factors Associated With Urinary Tract Infection in Young Febrile Infants', Pediatrics, vol. 116, no. 3, pp. 644-8.

Table 1 (on next page)

Sample Demographics and baseline characteristics.

Description of sample. HR, heart rate; AMA, against medical advice; IQR, interquartile range.

Variable	Total *n*	(%)	Not ill	(%)	Unsure	(%)	Ill	(%)	Not recorded	(%)
Male	1,498	(50)	718	(48)	143	(51)	141	(44)	454	(0)
Age median (months)	7.9		7.9		7.0		8.0		8.1	
Age IQR	2.7-13.6		2.7-13.6		2.1-15.3		2.5-14.7		2.6-14.1	
Ex Premature	316	(15)	209	(14)	44	(17)	63	(19)	121	(13)
Median weight (Z score)	-0.096		-0.033		-0.112		-0.33		-0.119	
Dehydration	341	(11)	55	(4)	56	(21)	128	(40)	102	(11)
HR >150	1875	(61)	937	(62)	165	(63)	223	(69)	550	(61)
HR >98th centile	978	(32)	483	(32)	84	(32)	125	(39)	286	(33)
Tachypneic	201	(7)	65	(4.)	19	(7)	50	(15)	67	(7)
Prior antipyretic	1430	(48)	791	(52)	124	(47)	128	(40)	387	(43)
Disposition										
Left AMA	0	(0)	0	(0)	0	(0)	0	(0)	1	(0)
Admitted	1175	(39)	463	(31)	125	(47)	203	(63)	384	(42)
Transferred	100	(3)	18	(1)	10	(4)	47	(15)	25	(3)
Discharged	1726	(57)	1029	(68)	129	(49)	496	(55)	496	(57)
Died	0	(0)	0	(0)	0	(0)	2	(1)	1	(0.1)

Table 2 (on next page)

Ordinal logistic regression model. The outcome variable is clincial appearance.

Clinical parameters associated with increased odds of moving from 'not ill appearing' to 'unsure' to 'ill appearing' categories. CI, confidence interval. Estimates derived using an ordinal regression model meeting the proportional hazards model assumption. This model shows that for each additional month of age the odds of a child moving up a category was 4%. Conversely as the child grew, and therefore weighed more, he was more likely to move down a category. Weight here is measured in quintiles, i.e. the first quintile represents the bottom 20th centile for weight the second quintile the 21st to 40th centile for weight (based on sample weight). *Included from an alternate but similar model. **Included in an alternate model as these exam findings may be sought in response to clinical appearance rather than informing the initial impression. The effect sizes of the other variables in these alternate models were essentially unchanged. The alternate models are shown in Appendix 2.

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Variable	Odds ratio	*p*-value	95% CI
Age (months)	1.04	0.011	1.01, 1.07
Quintile weight	0.81	0.008	0.70, 0.95
Dehydration	9.68	<0.001	7.17, 13.01
Pulse ≥150	1.31	0.021	1.04, 1.68
(Pulse >98th centile for age*)	1.25	0.076	0.98, 1.62
Tachypnea	2.44	<0.001	1.61, 3.68
Antipyretic at home	0.65	<0.001	0.52, 0.83
Antibiotics at home	2.56	<0.001	1.71, 3.82
(Meningismus or bulging fontanelle**)	7.28	<0.001	2.84, 18.64

Figure 1

Intensity of microbiological testing as a function of clinical appearance.

This illustrates increased intensity of testing in sicker appearing children. When unsure whether to classify a child as ill or well appearing clinicians obtained cerebrospinal fluid as often as if the child was ill appearing.

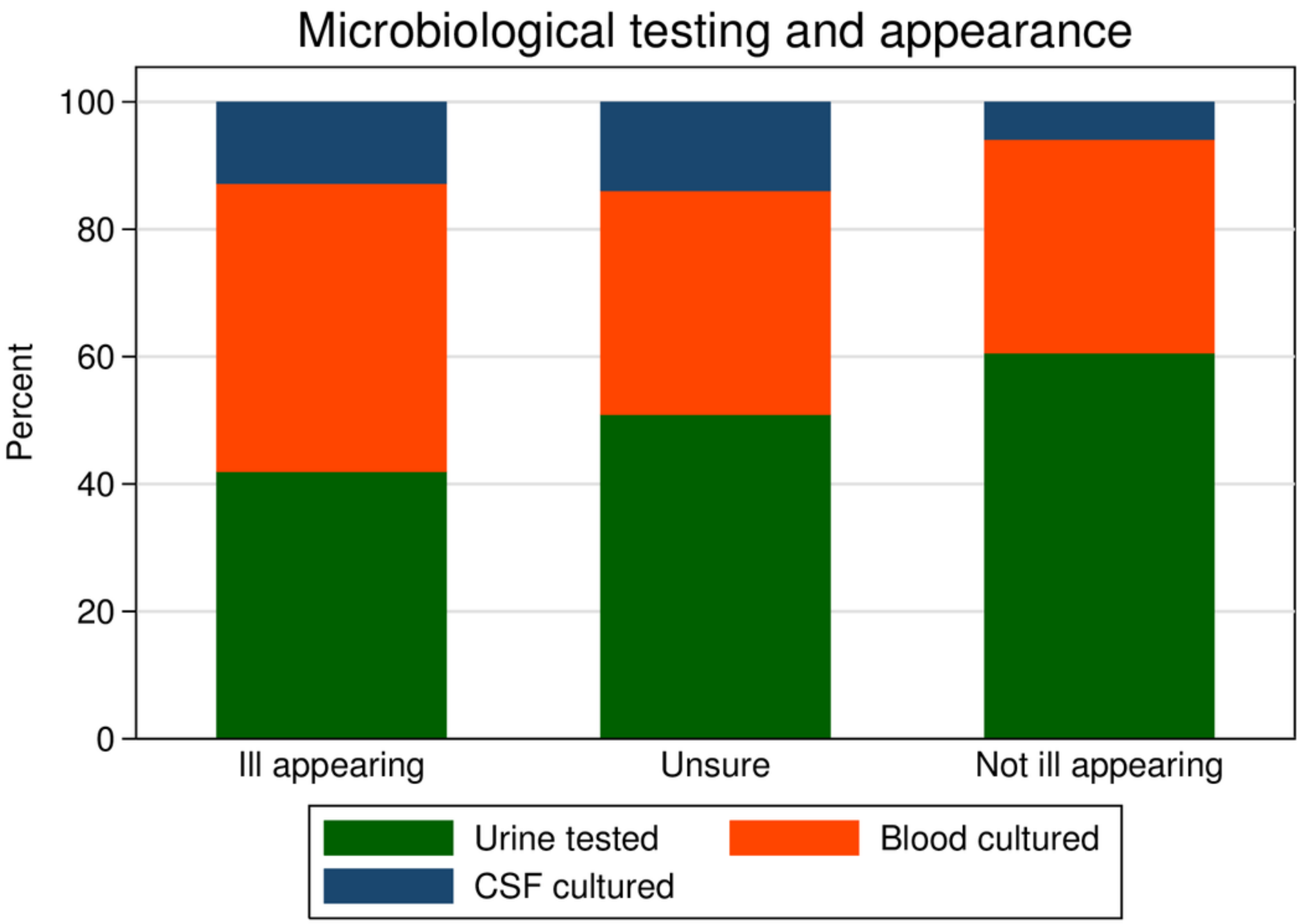

Figure 2

Clinical appearance and final diagnoses.

UTI; urinary tract infection, URTI; upper respiratory tract infection, NOS; not otherwise specified. Only the primary diagnosis is shown.

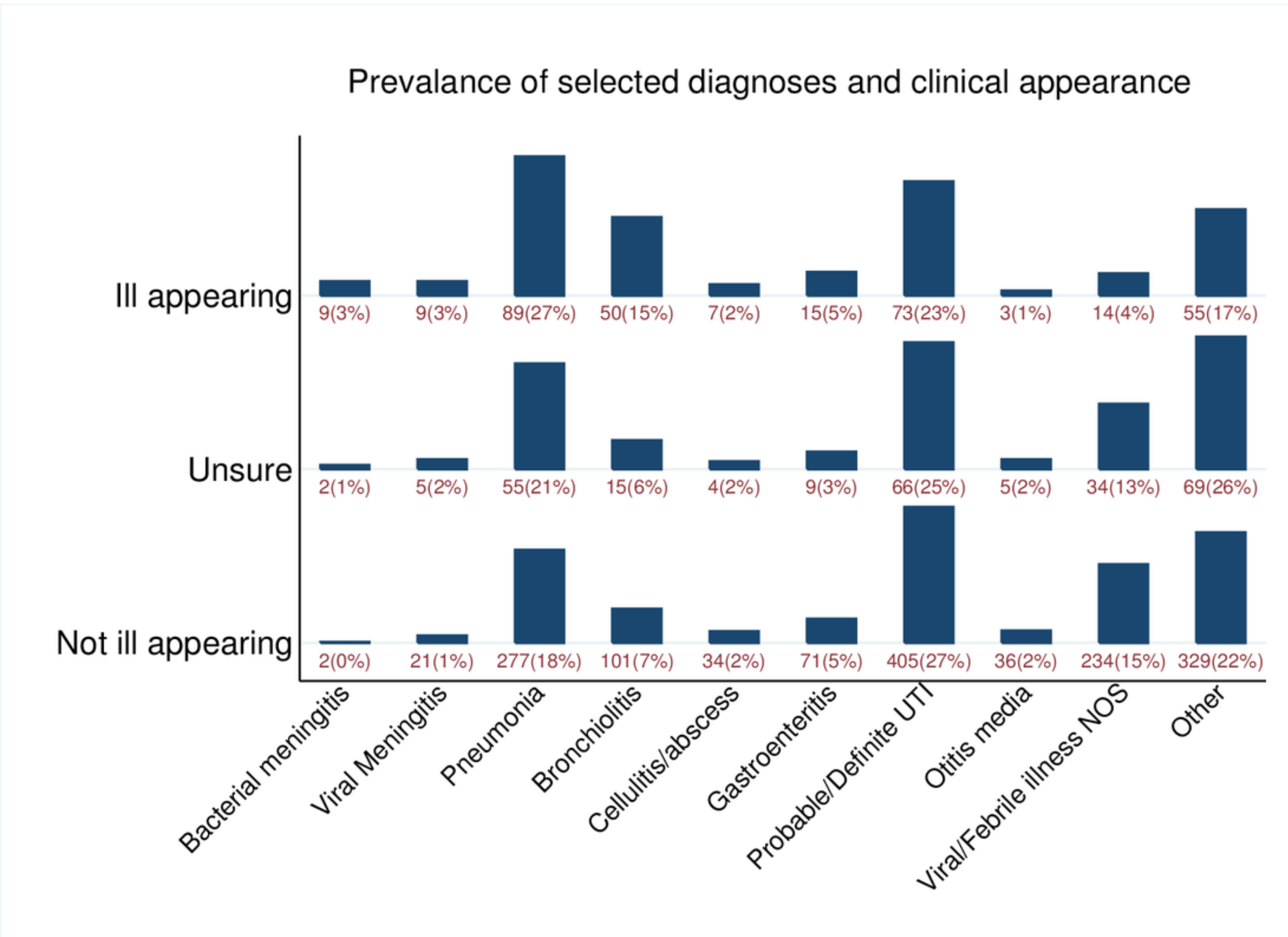

Figure 3

Overall clinical appearance and diagnosis.

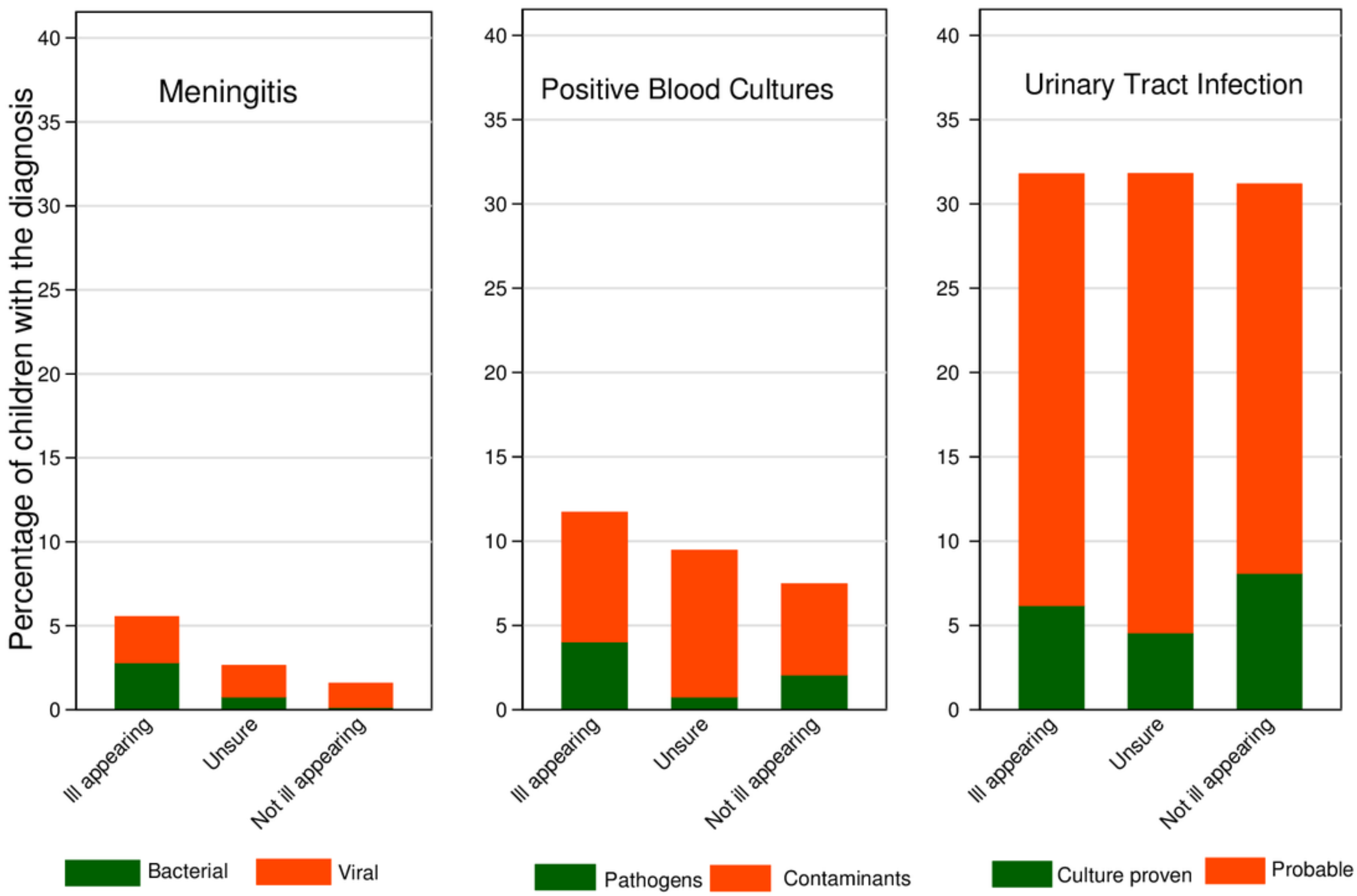

Figure 4

Clinical appearance and final diagnoses by age group.