



Child Health Research Project

Synopsis: Major Causes of Death in Young Infants

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Summary: This study represents the largest, multi center, prospective investigation of early infant infections in four developing countries—Ethiopia, The Gambia, Papua New Guinea and the Philippines—and changes our understanding of what pathogens are responsible for most neonatal death. Prior to this study, Klebsiella and Staphylococcus were thought to be the most important neonatal pathogens. In this study, however, Klebsiella was rarely cultured from the 4,552 infants under 4 months of age who were enrolled in the study. Other important findings include:

- *Streptococcus pneumoniae* was a major pathogen (20% of all isolates) in all age groups, and was particularly prevalent after the first week of life. It was the most important cause of meningitis, causing 50% of all cases,
- *Staphylococcus aureus*, was also found in 20% of blood isolates, and had a case fatality of 21%. Most of the cases of *S. aureus* (69%) were found in conjunction with scabies, and
- *Escherichia coli* and Salmonella were also important pathogens.

These findings emphasize the importance of having drugs to combat Salmonella (chloramphenicol or cefotaxime), in developing country formularies, and suggest that an antistaphylococcal penicillin, such as cloxacillin, be used in the initial therapy of neonatal sepsis in infants with pustular skin sores. It also underscores the importance of delivering conjugate pneumococcal vaccines to the developing world. This study also validated clinical signs used to predict serious infections in young infants which are now incorporated into the WHO/UNICEF's Integrated Management of Childhood Illness (IMCI) approach in 66 countries.

The World Health Organization estimates that 5 million children under one month of age die each year, and that nearly all (98%) of these deaths occur in developing countries⁽¹⁾. A large proportion of these neonatal deaths (3.4 million) take place in the first week of life⁽²⁾. Causes of neonatal death are often difficult to ascertain, because most of the births occur at home unattended by medical personnel. However it is known that the major cause of neonatal deaths are infectious diseases—which are associated with more than 40% of all early deaths (Table 1). Many cases of neonatal infection never reach treatment facilities, and the case-fatality rate for those that do ranges from 13 to 69%⁽³⁾. These survival rates could be improved by more accurate diagnosis of illness. Due to the limited availability of laboratory facilities in the developing world, identification and treatment of neonatal infections are largely based on history and clinical examination. Implementation of the WHO/UNICEF Integrated Management of Childhood Illness (IMCI) method has, in recent years, improved the identification of illness in children by training clinicians, nurses and local health workers to recognize validated clinical signs of serious illness and to refer children for treatment. Refinement of the IMCI approach for the health needs of very young infants requires further applied research on the cause of disease and death in this age group, as well as documenting the clinical signs to aid in diagnosis.

The Child Health Research Project's (CHR) support of the Young Infant's Study⁽⁴⁾ has provided comprehensive information on the etiology and clinical signs of serious infections in young infants in developing countries.

Specifically, the Young Infant's Study has:

- Identified the bacterial and viral agents responsible for serious infections in infants under 90 days of age in developing countries, and
- Recognized the simple clinical signs that best predict serious infection in infants under 90 days of age.

The Young Infant's Study, conducted by the World Health Organization, Department of Child and Adolescent Health and Development, examined 4552 sick infants under 90 days of age in 4 developing country institutions: the Medical Research Council Hospital, Fajara, The Gambia; the Ethiopian Swedish Children's Hospital, Addis Ababa, Ethiopia; the Research Institute for Tropical Medicine, Manila, Philippines, and the Papua New Guinea

Table 1. Estimated Global Burden of Disease: Major Neonatal Infections

Infection	Number of Cases	Case Fatality Rate (%)	Number of Deaths
Acute Respiratory Infections	2,500,000	30	750,000
Neonatal Tetanus	438,000	85	372,000
Sepsis	750,000	40	300,000
Diarrhea	25,000,000	.6	150,000
Meningitis	126,000	40	50,400

Stoll, BJ. The global impact of infection, in *Clin Perinatol* 1997; 24:1-21.⁽³⁾

Institute of Medical Research, Goroka. A fifth site in Latin America was abandoned in the planning phase of the study. The study began in September 1990, and continued until July 1993, when the final infant was recruited in Ethiopia.

To evaluate the importance of age in the patterns of serious infections in young infants in developing countries, infants up to 90 days of age were recruited. Infants were eligible for inclusion if their rectal temperature was 37.5° C or more, or 35.5° C or less, or if the infant displayed one or more of the following symptoms: cough; fast, noisy or difficult breathing; poor feeding; abnormally sleepy or difficult to wake; convulsions, or fever. Children excluded from the study were infants with routine clinic attendance (i.e. for immunizations); a chief complaint of trauma or burn; a newborn infant (less than 48 hours old) with a birth weight of less than 1500 grams; infants with probable nosocomial (hospital acquired) infections; sepsis, pneumonia or meningitis in the previous three weeks; transfer from another hospital; congenital malformations, or previous study enrolment.

If informed consent was received by investigators, children who met the study criteria were given a physical examination to assess the presence, absence and degree of severity of 51 clinical signs commonly associated with bacterial disease; a medical history was also taken. Oxygen saturation readings were taken when the children were in a resting state. After clinical evaluation, some infants underwent a laboratory evaluation that included blood culture, white blood-cell count, and a chest radiograph. Infants with a body temperature of above 38° C or below 35.5° C, or

clinical signs suggesting meningitis tended to receive a lumbar puncture. Pneumonia was diagnosed by interpretation of chest radiographs by a panel of pediatric radiologists in the US, UK and Switzerland. Decisions regarding treatment were made on a clinical basis. Most infants who were admitted to hospital were treated with penicillin and gentamicin parenterally. Treatment was adjusted according to clinical state, bacteriological and radiological results. Attempts were made to follow-up all infants 1 to 2 weeks after discharge, or 1 to 2 weeks after initial clinic attendance for infants who were not hospitalised.

The Gambia

Four hundred and seventy six infants met study requirements of the 695 who were triaged. The most frequently isolated pathogen from blood samples was *S. aureus*, which was found in the blood of 18 infants, and was the likely cause of death in 6 children. *S. pneumoniae* emerged as the most frequent cause of meningitis in young Gambian infants, causing eight cases of the disease. Three cases of invasive disease were found in infants younger than 2 weeks of age, which emphasizes the importance of this organism as a true neonatal pathogen. The organisms usually thought to be responsible for most cases of neonatal meningitis, *S. agalactiae* (group-B Streptococcus) and *E. coli*, caused only two of the fifteen cases during the study period. Salmonella infections were found in six children. Five of these six children with identified infections died, possibly because the usual regimen of treating serious infections in neonates (penicillin and gentamicin) is not effective against Salmonella. The importance of Salmonella as a neonatal pathogen raises the question of

whether ampicillin should be specifically recommended for the front line treatment of neonatal sepsis, or whether cefotaxime, or chloramphenicol, in appropriate doses, has a role in the management of serious infections in very young infants in developing countries.

One hundred and sixty one viruses were identified from 128 infants. Respiratory syncytial virus (RSV) and Influenza A were the most commonly identified viruses, and both peaked in frequency at the end of the wet season. Influenza B, parainfluenza, and adenovirus were also isolated in lower numbers. Infants with identified viruses tended to present at the first level health facility, and were less ill than infants with bacterial infections who were triaged at a referral hospitals.

Table 2. Antimicrobial Resistance of Pathogens in Ethiopia and Papua New Guinea

Country	Pathogen	Resistant to
Ethiopia	<i>H. influenzae</i>	Cotrimoxazole
Ethiopia	Salmonella	Cotrimoxazole, Ampicillin, Chloramphenicol
Ethiopia	Klebsiella	Cotrimoxazole, Ampicillin, Chloramphenicol
Papua New Guinea	<i>S. pneumoniae</i>	Penicillin (intermediate), Trimethoprim sulfate
Papua New Guinea	<i>S. aureus</i>	Penicillin

Ethiopia

Eight hundred and sixteen children were enrolled in the study, and 440 completed both laboratory and physical examinations. *S. pneumoniae* was the most frequently isolated pathogen, and was found in 10 of the 41 culture-positive infants less than 3 months of age. *S. pyogenes* was found in 9 infants, who were all less than 1 month of age. No group-B Streptococcus were identified. *E. coli* was found in ten children, nine of whom were in the first four weeks of life, and Salmonella was isolated in five children. *S. pneumoniae* and *H. influenzae* (3 isolates) were associated with pneumonia, sepsis and meningitis, whereas *S. pyogenes* and *E. coli* were associated with sepsis alone.

Antimicrobial resistance testing showed that *S. pneumoniae*, *H. influenzae*, *E. coli*, and *S. pyogenes* were mostly susceptible to the combination of penicillin G and gentamicin—the usual treatment for serious bacterial infections in this age group. *H. influenzae* isolates were resistant to cotrimoxazole (Table 2). All Salmonella and Klebsiella isolates, however, were resistant to ampicillin, chloramphenicol and cotrimoxazole—indicating the need for a carefully selected formulary of second-line drugs for children who fail to respond to initial therapy after forty-eight hours.

Seventy-four of the 202 infants tested were positive for at least one virus. Fifty-seven children had RSV; parainfluenza, influenza and adenovirus were also found. Studies for *Chlamydia trachomatis* were performed on 203 children, and 32 were found to be positive. Most cases of *C. trachomatis* were also found in children less than 1 month of age.

Papua New Guinea

There were 2168 children enrolled into the study, and of these children, 968 had clinical signs suggestive of severe infection. Most children (1817) were treated as outpatients, and no late fatalities were found in those children who were available for follow-up. Of the 343 children admitted, six died while hospitalized and another two are known to have died at home—yielding a case-fatality rate among admitted children of only 2%. A total of 856 blood cultures were examined, and after two days, 48 bacterial isolates were identified. *S. pneumoniae* and group-A Streptococcus each accounted for 13 isolates, and *S. aureus* was found in an additional 10 cultures. *E. coli* and *Klebsiella pneumoniae* were also identified in a total of five specimens. *H. influenzae* was only found in two of the 48 culture-positive specimens.

Group-B Streptococcus was rarely isolated in young infants, and in contrast to other sites in this multi center study, no Salmonella were isolated in Papua New Guinea.

The isolation rate of pneumococci from the blood increased with age and accounted for almost 50% of the bacterial isolates in the third month of life. Sixty-two percent of pneumococcal isolates were in serogroups 2, 5 and 7. Antimicrobial resistance testing showed that three of 11 pneumococci were intermediately resistant to penicillin and nine of 11 were intermediately resistant to trimethoprim sulfate (Table 2). Minimum inhibitory concentration (MIC) testing was also performed on 12 invasive strains of *S. aureus* and 10 were found to be resistant to penicillin, but all were sensitive to chloramphenicol and trimethoprim. This again indicates the necessity of carefully chosen second-line drugs for children who fail treatment with penicillin and gentamycin after 48 hours.

One thousand and twenty two nasopharyngeal aspirates were collected at the time of first clinical examination, and 86 specimens contained one or more viruses. Respiratory syncytial virus accounted for 42 of the viruses identified, and parainfluenza and influenza-A accounted for 26 and 10 respectively.

The Philippines

Between April 1991 and March 1993, 2053 infants were triaged at three community hospitals in Manila, and 873 had clinical features consistent with severe infection and were enrolled into the study. Of the 873 infants enrolled, 608 were forwarded for laboratory investigation, and 629 required admission to the hospital. Thirty-five children tested positive for bacterial pathogens in their blood or cerebrospinal fluid. The most common causes of neonatal meningitis in this population were gram-negative organisms, specifically *Acinetobacter* (4 cases), *E. coli* (2 cases), and one case each of *Pseudomonas aeruginosa*, *Enterobacter cloacae*, and *Haemophilus influenzae*—type b. Two infants with confirmed meningitis tested positive for *S. pneumoniae*. Three infants with pneumonia and three with sepsis tested positive for Salmonella. Case fatality amongst the culture positive patients was 26%. The most commonly identified viral pathogen was respiratory syncytial virus, which was found in 101 infants. Also commonly found were rhinovirus (59 cases) and adenovirus (24 cases).

The results of this study indicate that there has been a notable change in the pattern of infecting organisms in neonatal infections in the twentieth century⁽⁵⁾. Group-B streptococcus was not isolated at all in the Philippines, and rarely encountered in other sites of this multi-center study. In contrast, a retrospective review of charts of Filipino infants from July 1982 to December 1994, reported group-B Streptococcus as one of the most frequent etiologic agents⁽⁶⁾. This study also underscores the importance of evaluating standard antimicrobial therapy on a regular basis. Because Salmonella was the most frequently isolated pathogen, perhaps chloramphenicol instead of, or in addition to penicillin and gentamycin should be an option for the treatment of bacterial infections in Filipino infants.

Validation of Clinical Signs of Neonatal Illness

During the course of the multi-center study, clinical signs used to predict neonatal illness were tested. Comparing the infants' clinical histories and physical examinations with formal diagnoses based on laboratory and radiographic findings, the investigators produced a simplified clinical model to predict the presence of any abnormalities. The simplified predictive model used clusters of clinical signs, and included three vital signs (temperature, respiratory rate, and weight-for-age), the infant's age and five clusters of clinical findings: auscultation; (normal or abnormal heart-lung sounds) respiratory effort; evidence of neurological infection; inability to feed, and lethargy. The second part of the model was based on seven specific clinical findings: inability to suck, crepitations, (abnormal chest sounds caused by congestion in the lungs) cyanosis, history of convulsions, definite lower chest wall indrawing, failure to arouse with minimal stimulation, history of change in activity, and a group of vital signs: respiratory rate, age, temperature, and weight-for-age. Each of the clinical signs was assigned "risk points" which were then used to determine the probability of illness, and possible severity of the illness. For example, a four day old infant with a temperature of 37.9° C, respiratory rate of 76 per minute, weight for age Z score of 2 and crepitations would receive a total of 17 points and a probability of 34% of having at least mild hypoxemia, bacteremia or meningitis. The model is fairly accurate for the prediction of illness, and can be used by both physicians and non-physicians in clinical settings as a diagnostic tool.

Summary: Clinical Signs of Serious Infections

The WHO/UNICEF Integrated Management of Childhood Illness (IMCI) guidelines yield accurate identification of illnesses in outpatient settings, ensure more appropriate and combined treatment of all major illnesses, and provide speedy referral of severely ill children⁽⁷⁾.

In addition, the strategy also improves the counseling of caregivers and the provision of preventive services, and aims to improve the quality of care of sick children at the referral level. In the home setting, it promotes improved nutrition and preventive care, appropriate care-seeking behaviors and the correct implementation of prescribed care. As of year's end 1999, IMCI was implemented in 16 countries in the introduction phase; 34 countries in early implementation; and 16 countries in expansion phase.

Since the completion of the clinical signs portion of this study, the IMCI algorithm has been modified to include inability to suckle and inability to feed as indicators of possible serious infection in children under two months of age. Thus, the results of this study have been incorporated into diagnosis and treatment regimens in over 66 countries around the world.

Ongoing research will also provide more insight into the interaction of clinical signs predicting sepsis in this age group. These signs are planned to be prospectively validated in a series of further studies by CHR partners with the aim of identifying a small set of signs with good predictive power for severe disease in young infants. These validated signs will then be incorporated into guidelines for continued IMCI health worker training.

Figure 1. Positive Blood Culture Isolates

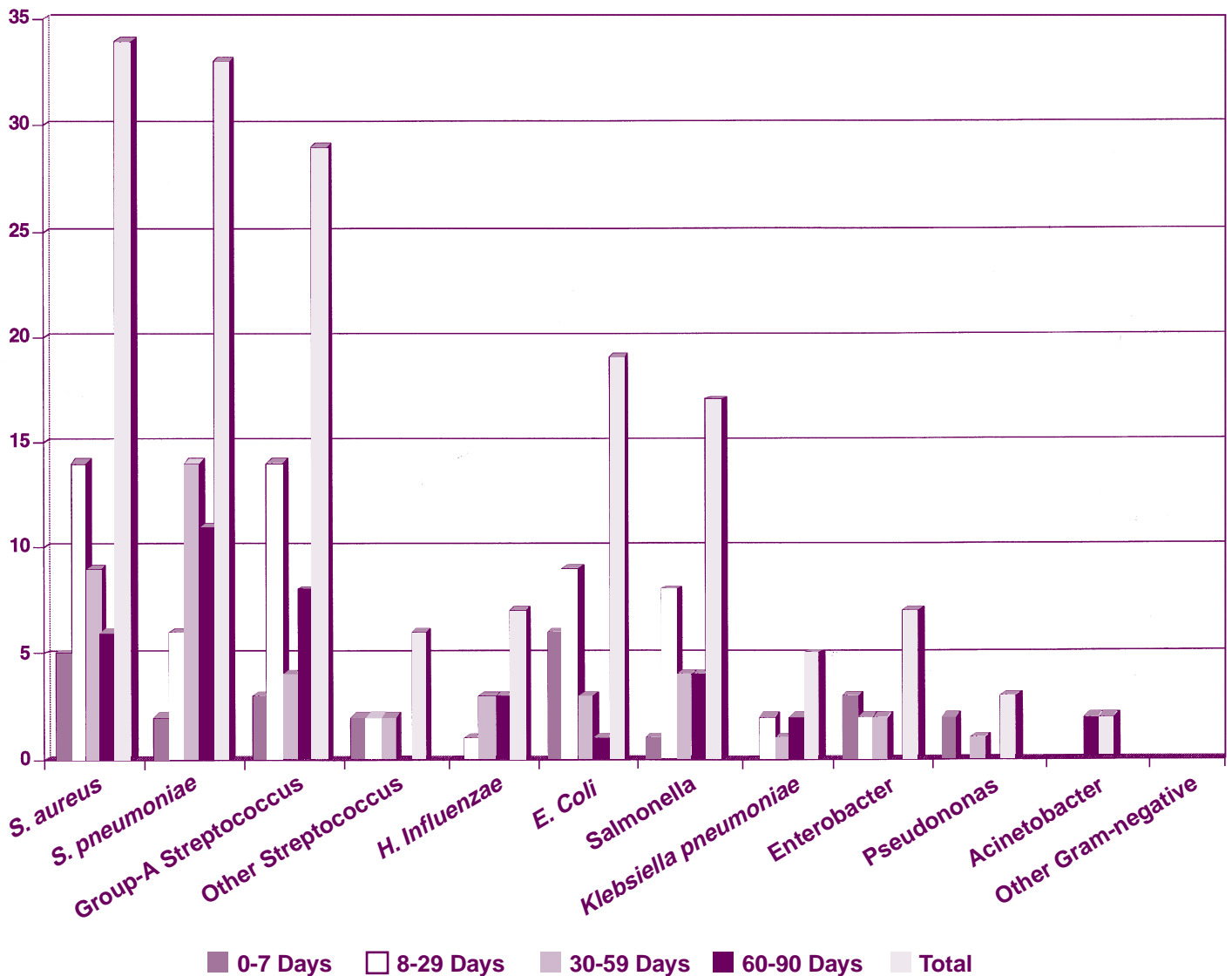
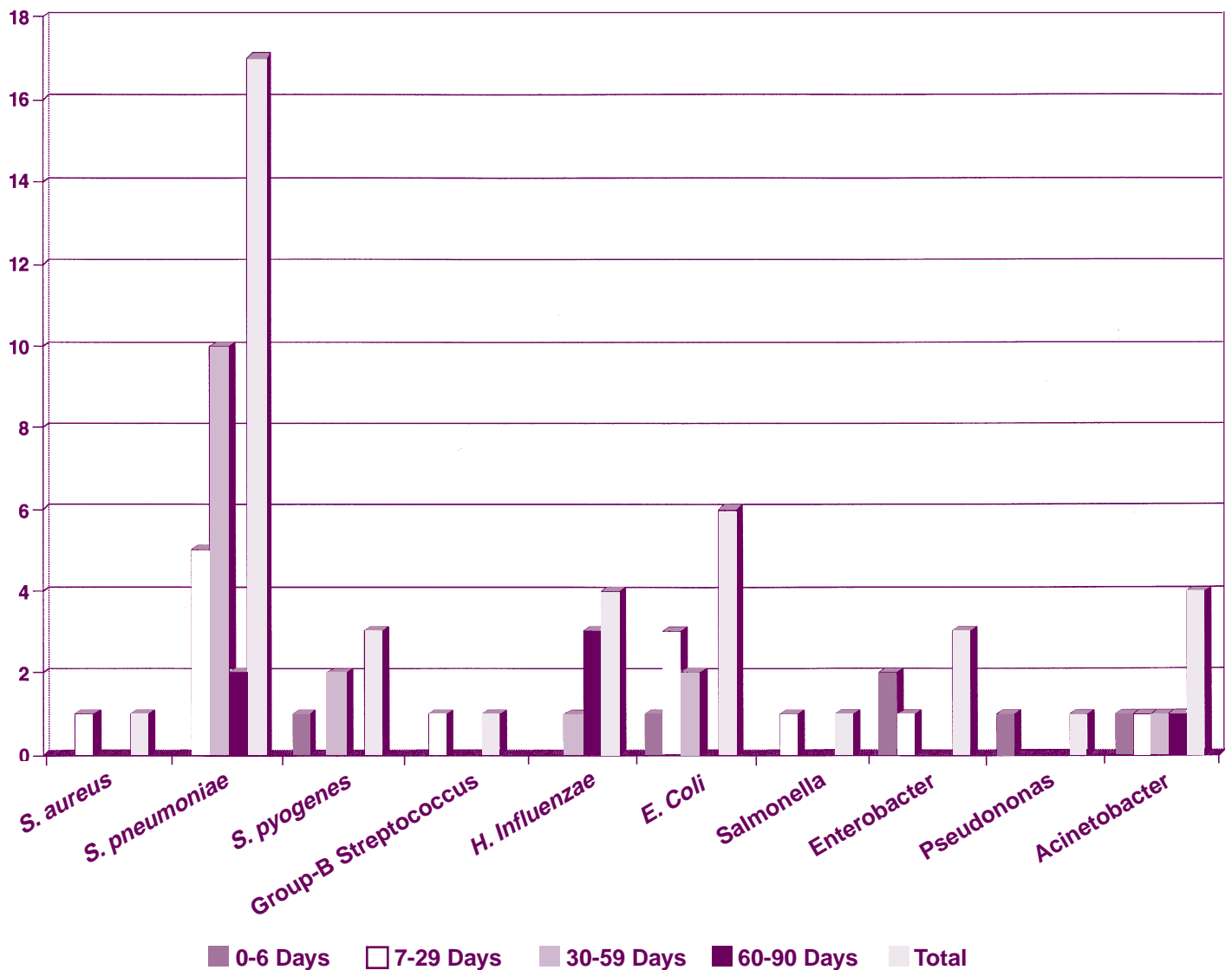


Figure 2. Positive Cerebrospinal Fluid Isolates



Summary: Etiology of Serious Infections

This study represents the largest, multi center prospective investigation of early infant infections in developing countries. Prior to the completion of this study, it was thought that *Klebsiella* and *S. aureus* were the most important neonatal pathogens in developing countries. In this study, *Klebsiella* was found in only 3% of the positive blood isolates, and no cerebrospinal fluid (CSF) isolates. Although this study, confirmed the importance of *S. aureus*, it was found in only 20% of blood isolates and only one CSF isolate. Most of the isolates of *S. aureus* were from The Gambia (69%) which was in the process of a scabies outbreak involving very young infants. Since the case fatality from *S. aureus* was so high in this study (21%), this finding suggests that an anti-staphylococcal penicillin, such as cloxacillin, should be

used in the initial therapy of neonatal sepsis in infants with pustular skin sores, or in communities prone to scabies outbreaks in this age group.

The importance of *Salmonella* as a pathogen in this age group is another important finding of this study, and emphasizes the importance of having drugs to combat this pathogen (chloramphenicol or cefotaxime), in developing country formularies.

S. pneumoniae was found to be a major pathogen in all age groups (Fig. 1 and 2), particularly after the first week of life, and it was found to be the most important cause of meningitis, especially in children older than one week of age, in whom it caused 50% of all cases. Sixty percent of all pneumococcal infections identified in this study could

have been prevented with adequate coverage using current conjugate vaccines. However, among the serotypes of *S. pneumoniae* found, the most frequently found was type 2 (26% of all isolates), which is not included in any of the current, commercially available pneumococcal conjugate vaccines. This finding supports the continued investigation of maternal immunization with the 23-valent pneumococcal polysaccharide vaccine as a strategy for controlling neonatal infections.

Future Directions

The threat to human health posed by antibiotic resistance is of growing global concern, with organisms resistant to multiple drugs as a cause of particular distress. The major selection pressures driving changes in antibiotic resistance are patterns and volume of drug use. Ongoing research by CHR and its partners has shown that targeted counselling and group discussions with physicians and pharmacists can decrease inappropriate prescribing of antibiotics and other medicines.

Prospective surveillance for major pathogens is desperately needed to adequately treat and prevent major pathogens in developing countries. Most data currently available is based on hospital surveillance. While useful, it is important to understand that many sick children die before ever reaching a health facility or hospital. Thus the need for community-level surveillance is of particular importance.

The findings in this study suggest a need for continued work on identifying the causes of disease and death in young infants, especially during the first week of life—an age cohort not currently addressed under IMCI. It is also necessary to further validate the clinical signs used to aid in diagnosis, treatment and referral. An increase in specificity of the IMCI approach (and a reduction in over-referrals) could also be achieved by reducing the number of clinical signs from 7 to 5. Additional studies are planned by CHR partners in several sites to study larger numbers of children in the first week of life. These studies will also be exploring community-based approaches to encourage mothers to recognize illness, and seek medical care for ill newborns.

Improved treatment for seriously ill young infants in developing countries is urgently needed. In most cases, this can be achieved with relatively inexpensive antibiotic drugs. However, this study shows that even with adequate care, the infant mortality rate was relatively high, emphasizing the overwhelming need to prevent these diseases, with improvements in perinatal care, birthing practices, early neonatal care and immunization.

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