

**SLIDE 1  Technical Seminar – Sick Young Infant**

In this technical seminar, I will describe the basis for developing separate guidelines for assessing, classifying and treating the sick young infant, age 1 week to 2 months. I’ll also explain why the newborn period was not included in the current IMCI guidelines. Finally, we’ll look at the results of WHO’s pivotal multi-center young infant study, which forms the technical basis for the current recommendations.

**SLIDE 2  Infant Mortality - Overview**

Over the past 35 years, we’ve witnessed several major improvements in global health. Between 1960 and 1990, “under 5" mortality in the world has been reduced by half, from 216 deaths per thousand live births to 107 per thousand live births (1).

Of the estimated 5 million newborn deaths each year, 98 percent occur in developing countries — the majority in Asia and Africa. Since most deliveries occur at home and reporting of neonatal deaths to health departments is consequently low, these estimates are likely underestimates. The major decline in infant mortality has occurred after the neonatal period — after 1 month of age.

To further reduce infant mortality, the causes of mortality occurring during the first month of life must be addressed. About 2/3 of the infant mortality occurs in the first month of life, and 2/3 of these occur in the first week of life (2).

The main causes of early neonatal deaths are asphyxia, birth trauma, infection, prematurity and malformations. During the remainder of the first month, deaths are due to sepsis, pneumonia, meningitis, diarrhoea disease and tetanus. Let me note that neonatal tetanus is declining as a cause of mortality — in fact, most of the decline in neonatal mortality is due to declining rates of neonatal tetanus. But in countries where the decline has leveled off, the rates of neonatal tetanus mortality have leveled off (3).
Here are some numbers related to infant mortality. Since most deliveries occur at home and reporting of neonatal deaths to health departments is consequently low, these estimates are likely underestimates.

For further declines to occur in neonatal mortality, perinatal causes will need to be addressed. Since these are primarily related to the process of delivery, the two will need to be addressed together.

As you can see from this slide, the highest mortality rates are in Asia and Africa, which account for 92 percent of all the neonatal deaths in the world. Neonatal mortality rates are expressed as rates per 1,000 live births (4). The neonatal mortality rates in Latin America and Oceania are about half that in Africa and Asia but about three times the rate in Europe and North America.

Since about 2/3 of these deaths occur in the immediate neonatal period, efforts at neonatal mortality reduction have to be coupled with efforts that improve maternal care during pregnancy, delivery and the postnatal period.

The main causes of neonatal deaths are asphyxia, birth trauma, infection, prematurity, and malformations. Some of the most important interventions, that are both relatively simple and cost-effective, can be implemented during delivery. Such interventions include practising clean delivery (5), basic newborn resuscitation when needed (6), prevention of hypothermia (7) and early and exclusive breast feeding (8, 9). Together with the management of syphilis (10) and tetanus vaccination, these interventions could reduce perinatal mortality substantially (11). However, these interventions would be most effective when deliveries are
supervised. Currently most deliveries occur in the home and are supervised by traditional birth attendants, or are unattended. Thus, newborn infants and the sick young infant would have to be brought to a health worker at a first-level health facility.

**SLIDE 6   Neonatal Mortality - Causes**

The single major cause of death in the neonatal period is infection, which accounts for about one-third of all the deaths. Birth asphyxia and birth trauma followed by prematurity/low birth weight account for almost half of the deaths, and congenital anomalies and other perinatal causes account for the rest.

Of these causes of death, birth asphyxia and birth injury can be prevented only with good antenatal care and safe supervised deliveries. The prevention of prematurity and low birth weight is the subject of many interventions, however, significant reductions of these problems on a large scale have proven to be very difficult without major improvements in the socioeconomic situation in these countries. Some neonatal infections can likewise be prevented by safe supervised deliveries. In the period before 7 days of life, perinatal causes of death are most important, while infections cause the majority of deaths later in the newborn period, from 7 to 28 days of age. This is one of the reasons for the application of the IMCI strategy only after the first week of life (12).

**SLIDE 7   Neonatal Mortality – Causes (continued)**

Infections make up a major portion of the preventable and treatable causes of neonatal mortality (13).

With the declining rates of neonatal tetanus, its primary role as a cause of neonatal death is becoming less important in most developing countries. The vigorous promotion and subsequent acceptance of exclusive breast feeding in the first 4-6 months of life have resulted in the lower relative importance of diarrhoeal diseases as a cause of mortality in the newborn period.
Of the treatable causes of death occurring after the first week of life, neonatal sepsis — including pneumonia and meningitis — tetanus and diarrhoeal diseases account for about 1.8 million deaths a year.

**SLIDE 8 IMCI Guidelines - Infection-Related Neonatal Mortality & Morbidity**

Directly or indirectly, IMCI addresses all the major infection-related causes of mortality in the young infant.

Simple clinical indicators have been used to identify and treat the young infant with serious bacterial infection — pneumonia, sepsis and meningitis — and diarrhoeal disease. The IMCI guidelines also address the prevention of tetanus with the maternal tetanus toxoid immunization.

One of the major problems of prematurity and low birth weight is difficulty in feeding. Even for babies where feeding problems do not endanger life, they contribute to delayed growth and development and may be one of the major predisposing factors for malnutrition in later infancy and childhood. The current IMCI guidelines address feeding difficulties.

In addition, exclusive breastfeeding in the young infant prevents ARI, diarrhoeal diseases and other infectious and nutritional diseases. The assessment and classification of breastfeeding problems, and breastfeeding counseling are also an integral part of the young infant section of the IMCI guidelines.

**SLIDE 9 IMCI Guidelines - First Week of Life**

Since a significant number of deliveries occur in the home, addressing the first week of life in IMCI guidelines would present many problems.

- First, the causes of mortality in the first week of life are very clearly related to the birth process and delivery. Interventions that provide for safe delivery are likely to have a bigger impact in this period of a newborn’s life.
• Most of this mortality can be prevented by interventions that achieve safe delivery and are much less amenable to treatment at a first-level health facility.

• The inclusion of the first week of life would entail expanding IMCI to include many preventive measures during labor and delivery (e.g., prevention of low birth weight and premature labor, resuscitation of the newborn, safe care when cutting the cord) that are beyond the scope of the current IMCI guidelines.

• The prevention of death from conditions such as low birth weight, prematurity, and hypothermia is intimately linked to maternal recognition of these conditions. Very few young infants are brought to a first-level health facility for these particular indications. However, they indirectly or directly account for a significant number of the neonatal deaths.

• In many countries, traditions keep the newborn baby at home for the first six weeks of life and the sick newborn infant is often not brought to a first-level health facility or to the hospital.

**SLIDE 10  WHO Multi-center Study - Rationale**

A significant proportion of young infant mortality is due to infections that can be responsive to therapy. However, a review of previously published literature revealed a lack of data from developing countries on the aetiology and clinical features of serious bacterial infection in young infants in developing countries (14).

Most of these studies were hospital-based, predominantly in the inpatient nurseries. As a result, there was little differentiation between community-acquired and nosocomially-acquired infections, and most frequently, gram negative bacteria were isolated from these newborns. There were few outpatient studies and none that adequately described the clinical features of serious bacterial infection.

The current IMCI guidelines are primarily for infants and children brought to first-level health facilities, and appropriate antibiotic choices need to be made for their treatment,
based on the prevalent micro-organisms. It is for these reasons that the WHO conducted a large study of the clinical features and etiology of serious bacterial disease in the newborn (13).

**SLIDE 11  WHO Multi-center Study - Description**

This study was conducted in **four centers in developing countries** — the Philippines (15), Gambia (16), Ethiopia (17) and Papua New Guinea (18).

This study included **4,552 sick young infants up to 90 days of age**, presenting to the outpatient departments of hospitals in these countries. **A complete history and examination** was performed on every infant, and all infants with certain criteria indicative of serious infection were investigated with blood cultures and CSF and other cultures as necessary. Chest radiographs and pulse oximetry was performed on some of the infants. The **outcome of every infant** enrolled in the study was recorded.

**SLIDE 12  WHO Multi-center Study – 11-item model to predict serious disease**

One of the principal objectives of the study was the **use of simple clinical signs that would enable health workers in developing countries to identify young infants at high risk of dying** (19).

Of the 4,552 infants enrolled 249, or 5.4 percent, died; 386, or 8.5 percent, had serious disease as indicated by positive blood or CSF cultures, CSF pleocytosis or an SpO2 less than 90 percent (hypoxia), and 450, or 9.9 percent, had mild hypoxia — SpO2 between 90 and 95 percent — or chest radiographic evidence of pneumonia.

Eventually a simple model employing weight, age, temperature, respiratory rate and five clinical signs were able to predict the presence of serious disease with a high degree of accuracy. An 18-item model comprising clinical findings and vital signs
was highly predictive of this ordinal scale. However, it was too complex to use in clinical practice.

A reduced 11-item model was almost as predictive as the more complex 18-item model. This reduced model included four vital signs such as age, temperature, respiratory rate, weight for age \( z \) score, and seven specific clinical findings: no arousal with minimal stimulation, history of change of activity, history of convulsions, inability to suck, definite lower chest wall indrawing, crepitations and cyanosis. Clinical findings were shown to be partial predictors of serious bacterial illness in infants.

**SLIDE 13** WHO Multi-center Study – Positive Blood Culture Isolates

There were 167 infants with proven bacterial infection (20), the commonest causes being *Staphylococcus aureus*, *Streptococcus pneumoniae* and Group A ß-hemolytic *Streptococcus* that accounted for about 60 percent of all positive isolates.

Surprisingly, gram negative organisms *E. coli*, *Salmonella* spp. and others accounted for a much lower proportion than previous studies had suggested.

Equally surprising, *Streptococcus pneumoniae* alone was almost as important as *E. coli* and *Salmonella* spp. combined.

*H. influenzae* accounted for less than 5 percent of all the infections.

**SLIDE 14** WHO Multi-center Study – Positive Blood Culture Isolates (continued)

The results of the positive blood culture isolates illustrated two important conclusions:

- The **gram positive cocci were more important** than gram negative bacilli in causing serious bacterial infections in the young infant.
S. pneumoniae are a significant cause of serious bacterial infection in young infants, a previously unrecognized observation.

SLIDE 15   WHO Multi-center Study – Clinical Features

Of the 4552 infants enrolled in the study, there were 2398 infants who were fully investigated in whom there was a 10% mortality 249 (5.4%) died (20). Mortality was highest in children with a positive blood culture at 31 percent, while 9 percent of those who were blood culture negative also died.

Death was associated with positive bacterial culture in the blood or CSF, those with major radiographic abnormalities, severe hypoxemia (SPO2 less than 90 percent) or an abnormally high or low white cell count.

The majority of deaths were in blood or CSF culture-positive neonates in whom the rate was greater than three times the rate in culture-negative infants.

SLIDE 16   WHO Multi-center Study – Gram Positive Organisms

Group A ß Hemolytic Streptococcus and Staphylococcus aureus, which were common causes of neonatal and puerperal sepsis in developed countries in the early 20th century, are important causes of neonatal sepsis and death in children in developing countries today.

Group B Streptococcus, which is the commonest invasive organism in developed countries, was rarely isolated in this four-country study (20).

Streptococcus pneumoniae was also a common organism isolated from children in this study with the highest mortality rate — 33 percent. The mortality rates with Group A ß Hemolytic Streptococcus was lower at 14 percent, probably because of its uniform susceptibility to penicillin.
The mean age of disease in children with gram positive organisms was between 33 and 47 days suggesting acquisition of these organisms in the home setting.

**SLIDE 17  WHO Multi-center Study – Gram Negative Organisms**

Gram negative organisms were less common than gram positives, however, the mortality was higher (35–53 percent compared to 14–33 percent) and occurred mostly in undernourished younger infants.

*Klebsiella pneumoniae* and other gram negative organisms, most commonly reportedly in hospital-based studies, were rarely reported from this multi-center study. This probably reflects the differences in etiology.

In the multi-center study, organisms isolated from sick young infants reflected the situation in the community. Most other neonatal sepsis studies in developing countries prior to this were hospital-based studies and probably reflected nosocomial transmission of bacteria.

In this study, the gram negative organisms are also isolated most commonly prior to the first month of life as opposed to the gram positives that were isolated in older infants.

**SLIDE 18 & 19  WHO Multi-center Study – Conclusions**

After the first week of life, infection is the most important contributor to high mortality in children in developing countries, specifically from pneumonia, meningitis and sepsis.

The most likely organisms are *Streptococcus pneumoniae*, Group A b Hemolytic *Streptococcus*, *Staphylococcus aureus* and *E. coli*. Group B *Streptococcus* and *Klebsiella pneumoniae* are uncommon causes of sepsis.

Based on their sensitivities to certain organisms, a combination of *benzylpenicillin* and *gentamicin* as a pre-referral antibiotic
would be the most appropriate to cover *Streptococcus pneumoniae*, Group A *Streptococcus* and *E. coli*.

Most *Staphylococcus aureus* are β lactamase producing organisms and are resistant to penicillin, and gentamicin has very little effect on *Staphylococcus aureus* in the absence of a specific cell wall active antibiotic. Where available, **cloxacillin** could be used to cover *Staphylococcus aureus* as well as other gram positive cocci.
REFERENCES


14. Stoll B. Personal communication


