

# Changing Pattern of Neonatal Diseases in Hong Kong

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**A**s Hong Kong emerged from an underdeveloped state to become one of the world's foremost financial centres,<sup>1</sup> significant changes occurred in child health.<sup>2</sup> Infant and neonatal mortality rates dropped sharply: infant mortality from around 100 per 1000 live births immediately after World War II to 3.65/1000 in 1997; neonatal mortality from 36 to 2.2/1000 live births over the last 50 years.<sup>3</sup> Patterns of neonatal disease have also shown dramatic changes during this period.<sup>4</sup>

Statements and data reported here are based on personal experience and medical records of our Paediatric Unit at Queen Mary Hospital (QMH) which, until 1995, was the only paediatric referral centre on Hong Kong Island, serving a population of 1.0 to 1.3 million.

## CHANGING CAUSES OF NEONATAL DEATHS

Hong Kong Health Authority statistics show that there have

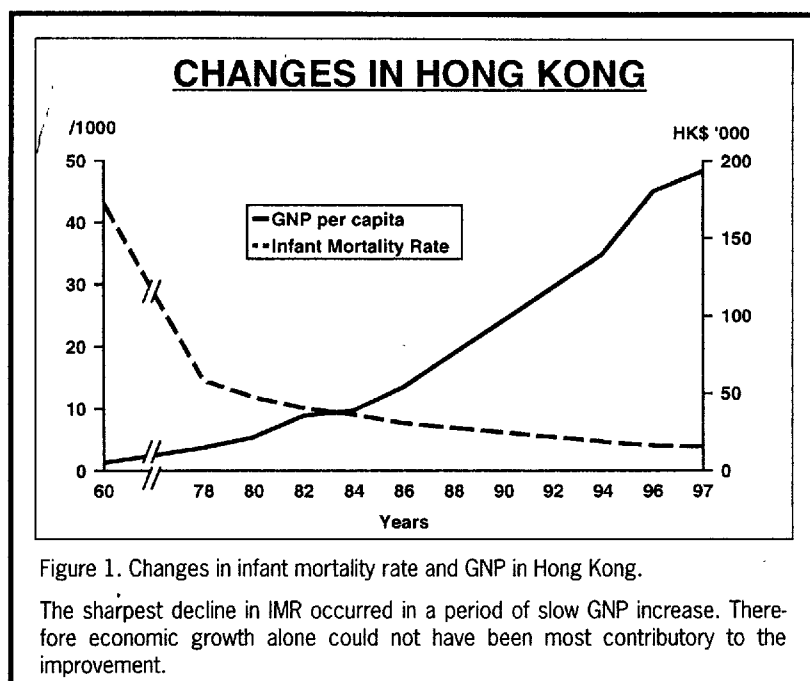


Figure 1. Changes in infant mortality rate and GNP in Hong Kong.

The sharpest decline in IMR occurred in a period of slow GNP increase. Therefore economic growth alone could not have been most contributory to the improvement.

been phenomenal changes in the leading causes of death among infants and neonates over the past 50 years.<sup>2,5</sup>

Interestingly, the most significant decline in infant mortality did not occur when GNP was increasing most rapidly. (Figure 1) Evidently, improvements in infant survival are not entirely due to improving economic conditions.

Other factors, such as effective immunisation programmes that have been able to eradicate many serious infections, must have played more important roles.<sup>6</sup>

Sixty per cent or more of all infant deaths over the past 35 years occurred during the neonatal period. In the early 1960s infection, low birth weight (LBW), severe neonatal jaundice (NNJ),

**Table 1. Leading Causes of Death (per 100,000 LB)**

Cause	1961	1976	1986	1997
Pneumonia	1092.8	179.6	40.0	21.5
LBW*/Prematurity	1070.3	251.7	192.5	72.9
NNJ, hydrops	191.2	158.6	100.0	4.9
Congenital anomalies	147.1	378.8	283.9	42.4
Asphyxia	133.1	175.6	65.1	16.6
All causes	3769.1	1430.4	738.1	404.1

\*LBW = All birth weights <2.5 Kg

**Table 2. Neonatal / Post-Neonatal Mortality (Per 100,000 LB)**

Items	1981	1986	1991	1997
Congenital anomalies	127/94	118/87	93/61	58/28
Born early (<37 wks)	187/10	130/9	93/11	36/8
Asphyxia	100/7	43/4	29/5	6/4
Perinatal problems*	132/11	85/11	55/25	16/6
<b>Total</b>	<b>575/271</b>	<b>383/170</b>	<b>284/172</b>	<b>130/114</b>
<b>Births</b>	<b>87104</b>	<b>72211</b>	<b>70135</b>	<b>60379</b>
<b>Population†</b>	<b>5.18</b>	<b>5.52</b>	<b>5.75</b>	<b>6.5</b>

\*Deaths due directly to perinatal problems, including infections

† = in millions

the actual decrease in neonatal and infant mortality over the last 10 years is even greater than the statistics seem to indicate. It is interesting to note that about half of LBW infants surveyed between 1970 and 1981 were also small for dates. By contrast the majority of LBW infants in recent years are born early and are of an appropriate size.

**NEONATAL JAUNDICE AND KERNICTERUS**

It is intriguing to note that 30 years ago jaundice, or haemolytic disease, was one of the top five leading causes of infant death. Rhesus iso-immunisation was rare as 99.9% of the local population was Rhesus D positive<sup>7</sup> and only a small number of infants who were hydropic due to  $\alpha$ -thalassaemia were born alive.<sup>8</sup> Sixty percent of the severely jaundiced infants did not have a haemolytic condition, apart from sepsis or other non-specific causes.<sup>9,10</sup> Most of the brain damage or kernicterus that caused death occurred in term infants rather than preterm infants, a feature which is very different to the West.<sup>9,11</sup> Some workers suggested that erythrocyte glucose-6-phosphate dehydrogenase (G6PD) deficiency was an important contributing factor. Earlier studies, however, showed that G6PD deficiency accounted for less than half of all cases of infant

congenital anomalies and birth asphyxia topped the list of causes of neonatal mortality. Nowadays congenital malformations and premature birth are the leading causes; neonatal jaundice no longer being a major cause at all. (Table 1) The most important causes of death over the last two decades have been congenital

anomalies, followed by premature births and perinatal hypoxia. (Table 2)

Before 1986, infants of less than 28 weeks' gestation or less than 1 kg birth weight were considered abortions. Infants with a birth weight greater than 500 g have only been included in the statistics since 1987. This means that

kernicterus.<sup>9-13</sup> Most of the other kernicteric term infants were jaundiced with non-haemolytic and non-specific conditions. Similar studies among other Asian communities have offered various explanations.<sup>12-19</sup>

Although exchange transfusion for severe jaundice was successfully performed in 1961, the first specialist neonatal department did not open until 1968.<sup>20,21</sup> With limited financial resources, efforts were focused on the prevention and management of severe neonatal jaundice. Even then, while it was known that this major cause of paediatric morbidity and mortality could be prevented and treated, financial constraints limited the purchase of phototherapy units. Alternative therapy had to be sought to handle a clinical load so huge that one study was able to recruit 1811 jaundiced infants in only 3 years.<sup>9,10,13</sup>

Oral phenobarbital, which induces liver enzyme activity, offered the basis for a highly effective and inexpensive therapy for neonatal jaundice.<sup>14,15</sup> Indeed through its routine and liberal prophylactic use, neonatal jaundice was brought under control.

It is sad to note that when Hong Kong's first special needs school, the John F Kennedy School, was established in 1965, the majority of the handicapped children admitted were survivors of kernicterus. In the late 1960s

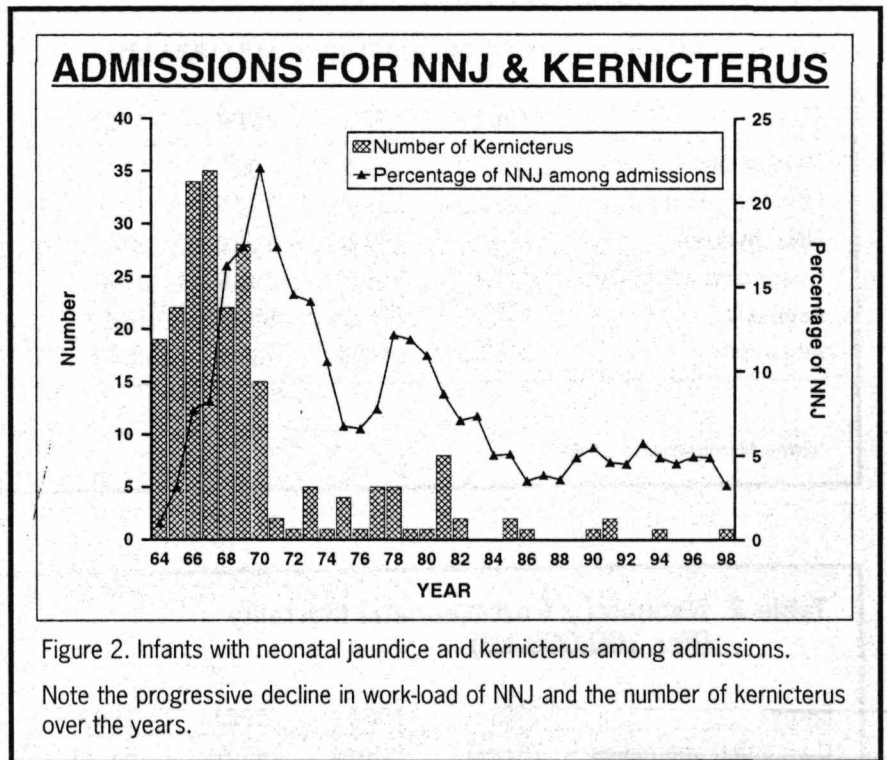


Figure 2. Infants with neonatal jaundice and kernicterus among admissions.

Note the progressive decline in work-load of NNJ and the number of kernicterus over the years.

and early 1970s it was common to perform 5 or more exchange transfusions daily in our hospital to prevent mortality and severe neurological outcome in survivors of neonatal hyperbilirubinaemia.<sup>9</sup> Today, barely one per month is performed.

Severe jaundice and kernicterus are no longer important causes of death, and hospitalisation due to severe jaundice has also greatly decreased.<sup>10</sup> Kernicterus, once highly prevalent, is also rare today.<sup>10</sup> (Figure 2) Studies indicate that the abandoning of at least two traditional Chinese practices could be strongly related to this trend: the practice of keeping the umbilical stump covered and

the use of herbal medicines for neonates.<sup>10</sup> Several common Chinese herbs have been linked with severe jaundice and kernicterus.<sup>16-18</sup> Some have been noted to precipitate severe haemolytic jaundice, especially in G6PD deficient infants.<sup>12</sup> Others, like "Chuen-Lin", "Ngau Huang" and "Yin Chen" are highly effective in displacing albumin-bound bilirubin from albumin. Excessive amounts of free-bilirubin displaced by these herbs, could produce kernicterus and other tissue damage.<sup>9,10,15-18</sup>

Keeping the umbilical stump of the newborn covered is a very deep-rooted Chinese tradition.<sup>23-26</sup> Various kinds of materials were

used to cover the umbilicus: from "umbilical powder of all sorts" to "ashes of burnt incense".<sup>23</sup>

Health workers had a hard time discrediting such a strong traditional belief. In the author's experience, the practice of keeping the umbilical stump exposed, dried and cleaned daily with an alcohol swab was not universally accepted until 1982. Such a change in practice might have contributed to a decrease in 'neonatal cholestasis' syndrome, 'cryptogenic splenomegaly' and portal hypertension as immediate and late complications of sepsis.<sup>27</sup>

It has recently been demonstrated that bacterial toxins and inflammatory cytokines, present at even sub-clinical infection levels, can enhance the cytotoxic effects of bilirubin in cell culture models.<sup>19</sup> These findings support our long-held suspicion that over-colonisation, eg. from an unhealthy umbilicus or unhygienic environment, could, in the past, have been partly responsible for the high frequency of kernicterus among term infants. The traditional practice of covering the umbilical stump would enhance bacterial over-growth and exposure to various bacterial toxins and inflammatory cytokines. The practice of exposing the umbilical stump and keeping it dry and clean with daily alcohol swabbing in all newborns, coupled with a reduction of herbal consumption,

has ensured kernicterus is now rare.

### NEONATAL INFECTIONS

Neonatal infection, as exemplified by pneumonia, has reduced significantly. (Tables 1 and 2) Where it was once the leading cause of death, by 1997, it was the third most common. In the past, most neonatal deaths were attributable to bacterial diseases caused by opportunistic organisms such as staphylococcus.<sup>22</sup> Improvements in socioeconomic conditions, education and healthcare facilities, availability of potent antibiotics, and implementation of infection-control systems in nurseries have contributed to the decline in neonatal mortality from bacterial infection. More serious conditions requiring increasingly sophisticated treatment are now more prominent causes of morbidity and mortality.

Although historical records of neonatal infections are unavailable for detailed analysis, recollection of past experience, departmental statistics and publications are all useful. A most notable change can be found in the prevalence of umbilical sepsis or omphalitis. Overt and sub-clinical umbilical infections were widespread and even neonatal tetanus from contaminated umbilical stumps was not infrequent as recently as the late 1970s. Neonatal tetanus has

disappeared and overt umbilical sepsis is now rare. Changes away from the traditional methods of caring for the umbilical stump may be responsible for this reduction in septicaemia.

Previously, sepsis due to multiple organisms was common. Staphylococcal<sup>22</sup> and other opportunistic infections frequently presented as mixed infections and could be responsible for pyogenic meningitis.<sup>28</sup> Adequate infection-control measures were not available in nurseries and even simple measures such as disposable paper hand towels were unavailable prior to 1981. Such practices strongly indicate that environmental contamination due to inadequate facilities or poor hygiene must have been the main factors contributing to neonatal infection.

Haemolytic Group B streptococcus (GBS) now ranks top on the list of causative organisms<sup>29</sup> and infection patterns now follow similar trends to those of more developed communities. This may be a reflection of the widespread adoption of more sanitary neonatal care.

Interestingly, *E coli* infection and meningitis complicating sepsis are not as commonly reported in the West. Among infants with early onset GBS infection, meningitis, fulminating sepsis and pneumonia are not uncommon, yet the overall mortality is much lower than that reported in other coun-

tries. In one study,<sup>29</sup> for example, mortality was reported as 7% while later studies reported fatality rates of 20 to 30%.<sup>30,31</sup> Studies conducted in our department indicate that the immune systems of local Chinese infants are more mature than those of Caucasians. Even premature Chinese neonates exhibited much higher cord blood IgG and complement levels;<sup>32</sup> their neutrophil functions were also noticeably more mature (except for chemotaxis).<sup>33</sup> This may explain their enhanced ability to contain infections preventing dissemination to other systems such as the central nervous system, and thus their improved survival.

Serological studies have shown that all local neonates possess high levels of IgG antibodies against CMV and EBV,<sup>34,35</sup> obviously derived from their mothers. Although all pregnant women must have been infected, congenital CMV infection occurs infrequently. The high degree of passive immunity from the mothers may also confer significant protection to the foetuses even though some mothers might develop a reactivation of the disease. Congenital rubella infections have occurred sporadically over the years, apparently related to the local government policy of vaccinating infants and 12-year-old girls but not boys, leaving many of them as reservoirs for spreading the disease. The policy was amended a few years ago

to include all 12-year old boys in the hope that rubella can be eradicated in the future. Congenital rubella syndrome was rarely encountered prior to the introduction of rubella vaccination, probably due to the high degree of herd-immunity.<sup>3,4,24,26</sup> Interestingly, there have only been a couple of cases of congenital toxoplasmosis reported in Hong Kong. Not a single case has been indentified in our group of hospitals in the past 19 years.

Sclerema neonatorum used to be a common condition, probably related to sepsis with resultant poor peripheral circulation as well as inappropriate cold exposure, but is now rarely seen.

#### CONGENITAL ANOMALIES

Congenital malformations were not carefully delineated in Hong Kong until the first cytogenetic laboratory opened in 1965. Since then there has been increasing interest in the identification of chromosomal aberrations and other malformation syndromes. Before, a number of neonatal deaths due to congenital malformation would have been classified as, for example, due to pneumonia—the secondary or terminal cause. Heightened awareness of congenital malformations probably accounts for the reported increase in frequency of deaths after 1970. (Table 1) The subsequent decline is

apparently related to the introduction of neonatal intensive care services in the 1980s, with increasing availability of new technology to sustain life.

In the author's experience some congenital malformations are uncommon in Chinese. These include congenital dislocation of hips, posterior urethral valve, renal agenesis and to some extent congenital pyloric stenosis.

#### BIRTH ASPHYXIA

It is gratifying to note the progressive and significant reduction in cases of fatal birth asphyxia over the years. (Tables 1 and 2) This is likely related to the availability of prenatal and antenatal monitoring equipment. The number of children with cerebral palsies has also shown a decreasing trend.<sup>36</sup>

#### RESPIRATORY DISTRESS SYNDROME

The number of premature infants with severe respiratory distress syndrome (RDS) necessitating hospital admission to the author's hospital has significantly increased over the past 30 years.<sup>6,37</sup> (Figure 3) Although this may be partly explained by improved survival of low birth weight infants, especially very low birth weight and extremely low birth weight infants, following the introduction of neonatal intensive care pro-

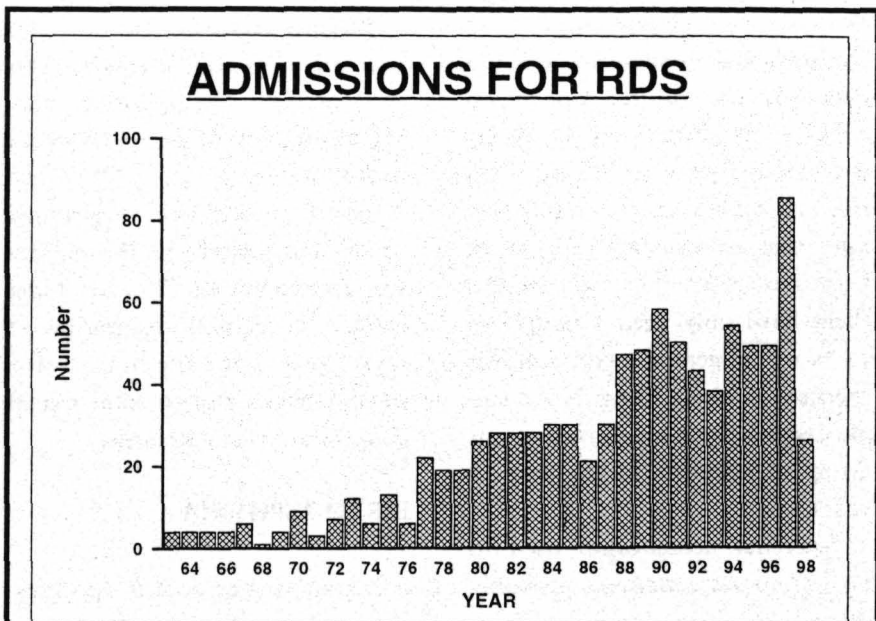


Figure 3. Infants admitted for respiratory distress syndrome.

Note the significant increase over the years; the decrease in 1998 appears to be related to the extensive and liberal prophylactic use of antenatal steroids.

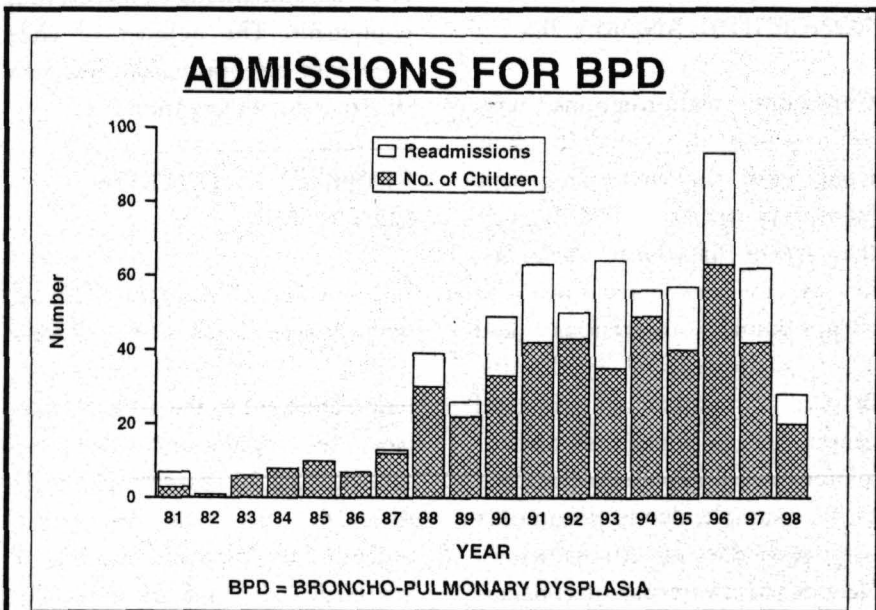


Figure 4. Infants with chronic lung disease (Bronchopulmonary dysplasia).

Note the initial increase that was due to improved survivals of VLBW and ELBW; and the plateau or slight decline, due to continued improvement of neonatal care.

grammes<sup>29,30</sup> the actual increase in RDS rate is disproportional to this improved survival.<sup>4,37</sup> Paediatricians who have spent time working in developing communities such as the Middle East have made similar observations. These physicians saw little RDS in these countries on their first attachment, but on returning to the same places in recent years they were surprised to see a significant increase in hyaline membrane diseases.

These observations strongly indicate there must be significant environmental or circumstantial factors at play. The author has suggested that improving socio-economic conditions, increasing standards of living with better housing and sanitation, improved nutrition and healthcare facilities may have contributed to the increase in RDS.<sup>4,6,36,37</sup> (Figure 3)

In an analogous instance, during the Vietnam War, veteran American paediatricians visiting Hong Kong were surprised to find few cases of RDS in our premature infants; this was similar to their experience in Vietnam. Many concluded that RDS was a genetic or ethnic related disease, rare (if not absent) among Orientals. These physicians were subsequently astonished to find RDS among the premature infants of the Vietnamese refugees who settled in North America. This indicates that the cause of disease is not genetic but related to



environmental factors. Although a change in diet could explain why RDS arose in this population, it seems more likely that hardships experienced by pregnant women during their life in their native Vietnam subjected their foetuses to significant and repeated intrauterine stress. Surviving foetuses would be sufficiently fortified to mount effective foetal adrenal responses enhancing the maturation of their surfactant systems and protecting them from developing RDS even when born prematurely. More recently, living conditions have markedly improved and the protective effect conferred by intrauterine stress has been lost. RDS has thus become more prevalent. This hypothesis appears to support observations of early investigators of the maturation pattern of the surfactant system; various intrauterine stresses are known to enhance the lecithin/sphingomyelin ratio of the amniotic liquor.<sup>38</sup>

Chronic lung disease (bronchopulmonary dysplasia) which was rare in the past, has become an important condition in Hong Kong over the last 18 years. Improved survival of VLBW and ELBW infants has resulted in a number of infants with this condition.<sup>39</sup> Despite its emergence, however, the disorder has not increased significantly over the last decade; there appears to be a decline in our hospital.

## SUDDEN INFANT DEATH SYNDROME

It has surprised many workers that sudden infant death syndrome (SIDS) is rare in Hong Kong Chinese infants.<sup>40</sup> Many have cited the traditional supine sleeping position of small infants as the reason; a number of studies show that the "back to sleep" campaign reduced the rate of SIDS.<sup>40-44</sup> Several additional factors have been identified to explain its rarity in Chinese.<sup>44</sup> One explanation is that Chinese foetuses are "better prepared to face the rough world." In one study, we have shown significantly higher cord blood IgG and complement levels in the early born.<sup>32</sup> In another study, neutrophil function was more mature compared with Caucasians (excepting chemotaxis).<sup>33</sup> These functions may make infants better prepared to face minor ailments such as pre-existing upper respiratory tract infections occurring before SIDS.<sup>45</sup> With improving standards of living and socioeconomic conditions, these 'protective advantages' may be gradually lost.

## CONCLUSIONS

The disease patterns for neonates in Hong Kong have changed significantly. Most of these changes appear to be related to improvements in socioeconomic conditions, education and avail-

ability of appropriate healthcare. Apart from certain genetic disorders, most neonatal conditions encountered today are similar to those seen in other developed communities.

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