OUTCOME OF DELIVERY AND CAUSE-SPECIFIC MORTALITY AND SEVERE MORBIDITY IN EARLY INFANCY: A KENYAN DISTRICT HOSPITAL BIRTH COHORT

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Abstract. It has proven very difficult to determine the causes of early infant mortality and morbidity in Africa. We undertook a two-year, prospective birth cohort study in a rural Kenyan District Hospital to estimate cause-specific mortality and severe morbidity in infants too young to gain benefit from routine immunization approaches. A total of 2,359 infants eligible for the cohort were delivered. Of these, 136 (6%) were stillborn and 77 (3.5%) subsequently died. Prematurity (34%), birth asphyxia (27%), and infection (18.5%) were the predominant causes of death in the first 98 days of life, although infection accounted for 36% of all life-threatening illness episodes in the same period. The data suggest that health system constraints are likely to impede programmatic efforts to reduce early infant mortality and morbidity, and that infection prevention measures offer some promise for mortality reduction. Assessing the cost effectiveness of the latter, particularly for very specific interventions such as further maternal vaccination, will require very large trials.

INTRODUCTION
Reducing perinatal and neonatal mortality is a major thrust of current international public health policy. Approaches to achieve this aim include, among others, the Safe Motherhood Initiative,1 the Integrated Management of Childhood Illness,2,3 and expanding the range of maternal vaccinations.4,5 Some of these interventions clearly require the presence of a functional first-referral level clinical facility to be effective. However, because the majority of births and deaths in this age group in resource-poor countries occur at home, the causes of death are often hard to establish. Indeed, in one community-based cohort study in Africa, it proved impossible to establish a cause of death in half of the infants dying in the neonatal period.6 Therefore, the potential impact of different interventions and the size of studies required to evaluate their true effectiveness are hard to gauge. This is particularly true for disease-specific interventions such as maternal immunization. We have therefore examined the outcome of delivery and the subsequent progress of infants born in a Kenyan district hospital to provide information on the workload presenting to a first-referral level hospital and cause-specific mortality and severe morbidity rates in infants too young to gain benefit from routine immunization approaches, a period prior to the protection that might be afforded by traditional vaccination regimens.

MATERIALS AND METHODS
The study was undertaken at the Kilifi District Hospital on the Kenyan Coast, the main government inpatient facility for a district of approximately 500,000 people, most of whom are subsistence farmers. During the study the hospital was staffed by two general medical officers supported by one specialist obstetrician/gynaecologist. Local estimates suggest that 80% of the deliveries occur at home (Were S, unpublished data). Neonatal and infant mortality rates for the community were estimated at 31.5 and 58.3 per 1,000 live births in 1992 and 1993, respectively.7 Provincial and national level data from 1998 suggest these rates are unlikely to have improved.8 The seroprevalence of immunodeficiency virus (HIV) is estimated to be 11% in urban antenatal attendees and 9% in rural antenatal attendees9 in the district. Malaria is endemic in the area with two annual peaks of transmission and subsequent disease from June to August and December to January.

Recruitment into the study took place between November 1999 and October 2001. Government policy during this period to date is that all pregnant women should receive two doses of tetanus toxoid, intermittent presumptive treatment of malaria with sulfadoxine-pyrimethamine, and that primigravidae should be advised to deliver in a health care facility. Short-course nevirapine therapy for prevention of mother-to-child transmission of HIV was not available during the study period. User fees as part of a cost recovery program were 20 Kenya Shillings (KSH, 20KSH = $0.3) for each antenatal or routine infant immunization visit, 500 KSH ($7) for a normal delivery, and 1,000 KSH ($14) for a caesarian section.

Women attending the district hospital for antenatal care at the Maternal and Child Health (MCH) clinic were informed about the study. All women subsequently delivering at the hospital were asked to consent to enrollment in an observational study of hospital birth outcomes by project assistants who provided 24-hour, 7-day-a-week coverage at the maternity unit. Mothers resident in a pre-defined study area extending approximately 30 km north, west, and south of the hospital were additionally asked if their children could be followed-up for the first 14 weeks of the baby’s life. The project assistants recorded maternal, demographic, delivery, and infant data, including progress to discharge, on standard questionnaires. Birth weight was measured with electronic scales (1583; Tanita, Kyoto, Japan) reading in 10-gram increments that were subject to weekly quality control checks. Infants were given a study-specific “road to health” card with a unique registration number.

The follow-up times were chosen to coincide with the Kenyan immunization schedule for diphtheria-pertussis-tetanus vaccination at 6, 10, and 14 weeks of age. The time before 14 weeks was considered a period of absent or imperfect protection from current primary schedule vaccination regimens and therefore was a target for protection by maternal vaccination. At follow-up the caretakers were interviewed and the babies were weighed. Infants who failed to return for vaccination/
follow-up within one week of their scheduled six-week appointment or two weeks of their 10- or 14-week appointments were visited at home. If the mother was unavailable or had moved, information at the home visit was sought from a reliable source about the status of the infant, and the date when the infant was last definitely known to have been alive was recorded. This date was used to censor time within the cohort.

Mothers of children who died at home were interviewed by a specially trained fieldworker using a neonatal verbal autopsy tool developed by the World Health Organization with minor local adaptations, and this questionnaire was used to assign cause of death.

If an infant was ill at or between review visits mothers were encouraged to bring them to a free, study clinic adjacent to the MCH clinic, open seven days a week and staffed by project clinical officers. All sick infants were reviewed with a standardized clinical questionnaire and admitted at the discretion of the attending clinician. Sick infants brought to the hospital and admitted outside these hours were identified with the aid of their study card through ongoing, 24-hour inpatient surveillance previously described. On admission, infants were further evaluated and investigated according to standard clinical protocols in place in the hospital and causes of admission and/or death, including deaths at home, were defined after review of all available data by the principal investigator (ME). The study was reviewed and approved by the Kenya Medical Research Institute Scientific and Ethics Committees, and all participants gave written, informed consent for enrollment.

Data storage and analysis. All data from study questionnaires were double-entered using in-built range and consistency checks and verified using Foxpro version 2.1 (Microsoft, Redmond, WA). Birth weight categories were defined to provide consistency with current definitions of low (< 2.5 kg) and very low (< 1.5 kg) birth weight and also to reflect a priori views on categories of risk. Stillbirths were categorized as fresh or macerated by the midwife attending the delivery. Perinatal mortality includes all still births and deaths in the first seven days of life. Neonatal mortality is defined as death of a live born infant in the first 28 days of life. Groups were compared using the chi square test, the t-test, and the Wilcoxon rank sum test as appropriate. Crude period prevalences for specific outcomes were calculated by dividing the number of events in a specified time period by the number of infants in the cohort at the beginning of that time period. Incidence rates were calculated within the prospectively defined infant cohort as the number of events per 1,000 days of follow-up. A combined rate of severe morbidity and mortality among infants discharged healthy from maternity was calculated. This rate thus excludes infants dying in the maternity ward and those admitted to the pediatric ward directly from the maternity ward. In all cases follow-up time was censored at a maximum of 98 days.

RESULTS

The progress of the 3,312 women and their infants approached for inclusion in the surveillance studies are described in Figure 1. Data from 3,189 mothers and their 3,305 infants were available for description of the total inpatient workload and immediate outcome of hospital delivery, while 2,283 mothers with 2,359 infants were resident in the study area and were therefore eligible for recruitment to the infant follow-up cohort. The characteristics of all the mothers attending the hospital for delivery and of these mothers according to eligibility for infant follow-up are shown in Table 1. Among mothers eligible for enrollment in the follow-up study (cohort mothers), 19% were either self-referred or formally referred because of a suspected obstetric problem compared with 33% of mothers ineligible for the cohort study (non-cohort mothers). The greater proportion of referrals among non-cohort mothers largely explains the differences between this group and that of the cohort mothers and their worse pregnancy outcomes (Tables 1 and 2). To provide some context to interpret these basic data, findings from the 1998 Kenya Demographic and Health Survey that describes the general characteristics of women delivering at home in Kenya nationally and household characteristics provincially are provided (Table 1).

The inpatient perinatal outcomes of all 3,305 infants born in the hospital are shown in Table 2. Of the infants of cohort mothers, 136 (6%) stillborn infants and 77 live born infants (3.5% live births) died during follow-up, 11 (14%) of these at home. Neonatal mortality among cohort infants was 30/1,000 (65 of 2,189) for all live births and 25/1,000 (52 of 2,049) for all single live births. These correspond to mortality incidence
rates of 1.1/1,000 infant days and 0.9/1,000 infant days, respectively, in the neonatal period. The crude period prevalence of death between 28 and 98 days was 0.5% (12 of 2,124) for all live births and 0.4% (7 of 1,982) for single live births. The respective mortality rates between 28 and 98 days were 0.09/1,000 infant days and 0.05/1,000 infant days. Among infants who neither died nor developed severe illness before the mother was discharged from hospital, 6% (135 of 2,112) either died at home or required admission (some subsequently died). This corresponds to a rate of life-threatening illness in infants discharged from hospital in a healthy state of 0.7/1,000 infant days.

A total of 229 live born cohort infants either died (n = 77) or were admitted but survived. All 229 infants in this group have been classified as having a life-threatening illness. The causes of death in live born infants and the causes of all life-threatening disease episodes are shown in Table 3. Prematurity (34%), birth asphyxia (27%), and infection (18.5%) were the predominant causes of death in the first 98 days of life (prematurity and asphyxia accounted for 40% and 32% of neonatal deaths, respectively). However, neonatal infection and pneumonia were together responsible for 36% (73 of 229) of all life-threatening illness in the first 98 days of life. The overall incidence rate for admission or death attributed to severe infection (excluding malaria and gastroenteritis) in the first 98 days of life was 0.5/1,000 infant days, although the rate in the first 27 days alone was 1/1,000 infant days. Age at death and age at presentation with a life-threatening illness or death if the child died at home are shown in Figure 2. Within 14 days of delivery 75% of the deaths and 65% of all life-threatening episodes have already taken place.

DISCUSSION

The data presented address three issues. First, they provide information on the current functioning of a district hospital maternity unit serving a predominantly rural community in Kenya. Second, and indirectly, they shed further light on the likely causes of neonatal and early infant mortality more widely in such an environment. Finally, they provide estimates of mortality rates and severe infection specific morbidity rates, albeit in a hospital-based cohort, that might be used as the basis for evaluating interventions. The perinatal mortality rate in the hospital of 9.5% of all delivered infants is at first sight disturbingly high. However, 44% of these perinatal deaths were either macerated stillbirths or deaths due to premature delivery, while even when the outcome was a fresh...
stillbirth in 70% of the cases, a fetal heart was not detected on admission to the maternity unit. The data therefore suggest inadequacies in the referral system, as well as in referral care, and that parallel improvements in both areas will be required to reduce perinatal mortality.

Hospital-based data must be interpreted cautiously when discussing the pattern and cause of morbidity and mortality in countries such as Kenya where the majority of deaths occur at home without a cause assigned. Are the data therefore of any general value? A network of more than 200 government and non-governmental hospitals of similar capacity to our hospital provide first-referral level care to largely rural populations in Kenya. The seroprevalence of HIV nationally is estimated at 13%, close to that for Kilifi District (10%). Our data may therefore be representative of a sizeable sector of the health care system in Kenya. Observed neonatal mortality was similar to that in previous community-based estimates in Kenya and unlike previous community-based studies, the cause of death and severe illness were established in all cases. The data indicate that prematurity and birth asphyxia account for 62% of early neonatal deaths. Although differentiating prematurity and intra-uterine growth retardation is not straightforward, the cause of death in this study was assigned by an experienced pediatrician, and the major contribution of prematurity to neonatal mortality is consistent with recent community-based data from sub-Saharan Africa. When considering the possibility of selection bias in our population, it may also be worth noting that only 3% of the hospital births in our cohort weighed less than 2 kg. Among non-Hispanic black Americans, 3% of all infants weigh less than 1.5 kg at birth and 4% are thought to be born at less than 32-weeks gestation.

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A feature rarely described in community-based studies is...
but highlighted by our data is the rapidly increasing risk of death with increasingly marked forms of prematurity/low birth weight. The importance of a major contribution to overall neonatal mortality made by sub-populations at very high risk has recently been discussed. The principal implication is that health intervention strategies that have as their aim an increase in mean birth weight are unlikely to have a major impact on overall mortality unless the specific, at risk sub-populations also benefit directly from the intervention. Conversely, effective interventions narrowly focused on high-risk groups may have a significant impact on overall mortality rates. Recent encouraging experience with a hospital-based essential clinical care package for the newborn in Papua New Guinea is therefore of interest.

Although severe infection was a prominent cause of mortality in infants less than 98 days old in this cohort, its total contribution amounted to less than 20%. Possible support for a more major role among deaths in the community is suggested by the fact that suspected neonatal sepsis and pneumonia together were responsible for 36% of all severe illness events in the first 98 days of life. While severe infection therefore appears to provide a promisingly large target for intervention, current information on etiology indicates that no one organism markedly predominates. The range of pathogens and the findings that placental malaria infection (common in our setting) and prematurity/low birth weight may reduce the transfer of antibody to the newborn all limit the potential effectiveness of prevention through maternal vaccination. This suggests that general protective measures and perhaps system-strengthening interventions might be more effective.

Reducing perinatal and early infant mortality, which together are often responsible for half of all infant mortality, is a major public health challenge in resource-poor countries. The complexity of the problem suggests that small incremental gains are more probable than the rapid, large improvements that may initially be hoped for. A sound, sustainable health service delivery mechanism incorporating community care linked to peripheral and referral level care seems an essential component of many proposed programmatic interventions. Our observations at the first referral level suggest that without further support current capacity may be inadequate to meet fully the demands of implementing such interventions.

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