Mortality and Infectious Disease Associated with Infant-Feeding Practices in Developing Countries

Janine M. Jason, MD, Phillip Nieburg, MD, MPH, and James S. Marks, MD, MPH

This review examines the available studies bearing on the relation between infant-feeding mode and infectious illness in the populations of less-developed countries.

A companion critical review of studies of the relationship of infant-feeding methods and infection in industrialized countries has concluded that, although laboratory studies provide biologic plausibility for a lower infection rate in breast-fed infants, an effect, if present, is apparently modest.[39] The strongest evidence for a protective effect of breast-feeding in industrialized countries is for gastrointestinal (diarrheal) illness. In this review of studies among populations in developing countries we found the evidence for an important protective effect of breast-feeding against infectious illness to be much stronger. This conclusion was reached despite serious problems in the design of many of the studies reviewed.

One characteristic that distinguishes populations in less-developed countries from those of industrialized ones is the infant mortality. Even today, infant mortality for much of the world is up to ten times higher than infant mortality in the United States and Northern Europe.[46] This undoubtedly reflects differences in sanitation, nutrition, housing, and other indicators of socioeconomic status. Much of the difference in rates of infant and child mortality and morbidity is attributable to high rates of infectious illness, especially gastrointestinal disease. Thus, in these populations, the positive effects of breast-feeding are of greater potential importance for the health of the infant population and should be easier to detect in clinical and epidemiologic studies.

In this review we will address the following key questions: (1) whether the method of infant feeding (breast *v* other) is associated with differences in rates of mortality, both overall and infectious, and in rates of infectious morbidity in less-developed countries; (2) whether differences exist between breast-feeding and other feeding methods in terms of infection rates for specific pathogens; and (3) whether the evidence is strong enough to suggest that any association is a causal one, ie, that the effect noted is actually caused by breast-feeding rather than other factors associated with rates of illness.

The review will not address the question of immunologic mediators of protective effects except in those studies in which such mediators were directly linked to clinical illness. Analysis of the available studies follows general methodologic guidelines.

Important methodologic details of study design were frequently lacking. These included: (1) control for those factors other than feeding method (eg, socioeconomic status or birth weight) that could affect outcome; (2) descriptions of what constituted a clinical diagnosis, such as gastroenteritis/diarrhea; and (3) indication of reasons for choosing or changing a given method of feeding.

The few studies that have directly addressed any of these issues are discussed in this report. The accompanying tables outline each study's structure including its design. In several investigations, authors did not calculate the risk ratios associated with method of feeding; in others, statistical significance was not estimated. In those reports where the raw data were available and the results of such testing were not provided, we calculated the appropriate summary statistics (although we recognize the limitations of such univariate analyses). These secondarily calculated values are so indicated by an asterisk (*). A few studies from developed populations are included when they relate to the potential effects of breast-feeding on infections with specific pathogens or in specific organ systems.

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OVERALL MORTALITY AND MORBIDITY

Overall Mortality

A number of studies in less-developed countries have considered whether breast-feeding is associated with lower mortality than is bottle-feeding. For the sake of clarity, we have reviewed first those studies that support an inverse association between breast-feeding and mortality and then those that fail to find this association.

Mata et al[44] prospectively examined mortality in the first year of life among a cohort of 625 infants in a rural area of Costa Rica during September 1979 through September 1980. A subcohort of children (n = 286) was followed more intensively, with health care visits through 1981. The area was targeted for a program of education encouraging breast-feeding during the period 1975 through 1980, and increasing rates of breast-feeding in the study area, compared with rates for all of Costa Rica, were documented. For the same period, infant mortality was said to have dropped proportionately more in the study area than in all areas of Costa Rica, from 38/1,000 to 4/1,000 *v* from 37/1,000 to 22/1,000. At the time of data analysis, all study infants had not yet reached their first birthday. The investigators also reported a 38% reduction in hyaline membrane disease and explained at least part of this reduction on the basis of increased breast-feeding. They did not directly compare mortality in breast-fed infants and formula-fed infants, nor did they discuss other changes that might have occurred during this period, eg, improved maternal nutrition, improved sanitation, or education concerning water sterilization or oral rehydration.

Cantrelle and Leridon[8] retrospectively surveyed the outcome of 8,456 live births in Senegal between December 1962 and March 1968. Data on age at weaning and mortality were obtained through annual household interviews. Eight weaned children died. The authors found the weaning age to be greater for those who died between 2 and 4 years of age than for those living at that age. They suggested (but did not present supporting data) that weaning was postponed for children who were ill. No difference in mortality was found at 0 to 8 months between those weaned and those breast-fed, but the reported numbers of infants weaned at these ages were extremely low. Mortality was 50% to 150% higher for those few infants weaned because of the mother's subsequent pregnancy than for the general childhood population. Other reasons for weaning were not discussed. The authors concluded that in a setting where breast-feeding was nearly universal, it was associated with lower mortality, but only when compared with mortality among those weaned because of the mother's subsequent pregnancy. Furthermore, prolonged breast-feeding might have been associated with increased mortality although whether weak or ill children were given prolonged breast-feeding as a health measure was not known.

McKenzie et al[47] did a retrospective case-control study of child mortality in Jamaica. Cases were a 10% random sample of death certificates of children 6 months through 3 years of age (sample n = 285, completed questionnaires on 204 or 72% of sample). Questionnaires were completed on 154 (56%) of 273 control subjects, who were living contemporaries matched, on the basis of birth certificate data, for sex and month of birth. Among those with known feeding history, full breast-feeding after 6 months was reported slightly more frequently among control patients (34/134, 25%) than among cases (23/137, 17%). This difference was not statistically significant.

Scrimshaw et al[63] did a prospective study in 11 rural villages of northern India. Four successive yearly cohorts were followed from 1 to 4 years; thus, although all children were followed throughout the high-risk period of infancy, the older cohorts had a lengthier evaluation. Artificial feeding consisted of cow, goat, or buffalo milk, with solids added at 6 to 12 months. The infant mortality (defined as the rate from 0 to 11 months) was 950/1,000 live births in the artificially fed group and 120/1,000 in the breast-fed group. The authors, noting the high mortality among infants who were bottle-fed from birth (19/20), explained that ten of these infants were fed this way because of "weakness." They did not otherwise address the important question of comparability between breast-fed infants and artificially fed infants. The nutritional inadequacy of the described artificial-feeding formulas suggests that the higher mortality among the bottle-fed infants might have been related as much to nutritional status as to infection.

In a Cairo, Egypt, hospital, Janowitz et al[35] interviewed 2,907 women at parturition about their previous child. Because women giving birth in hospitals accounted for only 35% of childbearing women in urban Egypt, the representativeness of the feeding and mortality experience of this group is questionable. The authors used a multiple regression analysis that included the mothers' age, education, geographic location, obstetrical history, and the infants' breast-feeding status at 3-month age intervals. Up to 1 year of age, breast-feeding was found to be associated with a 29% increase in survival.

Plank and Milanesi,[57] in an often-quoted survey conducted in rural Chile, questioned 96% of all females aged 15 to 44 years in 15 communities about their last live-born infant who was born in the past 5 years and had survived at least 4 weeks. The authors found the mortality between 3 and 12 months of age was nearly three times as high in infants exclusively bottle-fed at 3 months of age (16/413) as in those exclusively breast-fed at 3 months of age (11/798) ($P < .01$). Mortality was only slightly less in those fed both breast milk and bottle feedings than in those fed by bottle alone. The addition of nonmilk food decreased mortality at 13 to 38 months. The authors suggested that these data were more consistent with the belief that breast-feeding enables avoidance of disease associated with bottle feeding than with a protective action of breast milk itself. However, their results are equally consistent with the possibility that breast milk provides primary protection which requires a threshold intake of breast milk. These authors did examine certain potential confounding variables, including maternal age and parity. They stated that mortality increased with increasing sanitation, income, and maternal education, and suggested that this was perhaps attributable to the association they found between these variables and early weaning.

Goldberg et al[25] analyzed data from a family planning/maternal and child health survey in northeast Brazil. In 1980, they interviewed 7,852 females aged 15 to 44 years about their most recent live-born child (n = 5,190). All children who were born more than 1 year before the interview and who had survived more than 1 month were included (final n = 3,457). Feeding status was dichotomized, on the basis of the mothers' own definition, as ever breast-fed or never breast-fed. The authors used a linear logistic regression analysis including mother's urban/rural status, education, current employment, age at last birth, time since last live birth, and use of maternal and child health services. For ages 1 month to 1 year, infants who had never been breast-fed were found to have a mortality 1.7 times higher than that of breast-fed infants ($P = .001$). The effect of breast-feeding was greater in rural than in urban areas and other factors (eg, maternal prenatal care, employment, or education) appeared to be at least as important as feeding status.

Butz et al[7] did a complex analysis of data from the 1976–1977 Malaysian Family Life Survey to look at the effects of breast-feeding in the first year of life. They used the age intervals ≤1 week, 1 to 3 weeks of the first month, 1 to 6 months, and 7 to 11 months. Mothers were questioned about each live birth. (Including all living children could differentially increase the risk of recall error for data on older children. This could have important effects upon results if there were secular trends in breast-feeding prevalence.) Deaths were assigned an imputed length of breast-feeding to prevent attributing cause of death to discontinuation of breast-feeding when, in fact, a third factor (illness, for example) may have caused both the discontinuation and the death. Sanitation, maternal age, maternal education, birth weight, birth order, and feeding status were included in the analysis. Results were largely derived from a linear probability model estimated by ordinary least squares. Birth weight was found to be the most significant factor in mortality. Breast-feeding had a significant protective effect that was greatest with full breast-feeding in the first month of life. When the interactive effects of sanitation and breast-feeding were assessed, the risk associated with non-breast-feeding was found to be greater when the household lacked a toilet than when it lacked other forms of indoor plumbing. As noted by the authors, none of the regression coefficients, including that of breast-feeding and mortality, were very high.

In a frequently referenced study, Dugdale[17] reviewed 20 years of medical records (1953 through 1972) in an isolated Australian aboriginal settlement and could detect no protective effect associated with breast-feeding. Five individual years were selected for assessment of effects of breast-feeding. Infant mortality declined between 1955 and 1959, and between 1968 and 1972; rates of breast-feeding declined from 1953 to 1963 and rose again between 1963 and 1972. The village was said to have received virtually no public health intervention measures during this time. Using "number of infant-months" of feeding by breast or bottle as the denominator, Dugdale found a lower mortality among breast-fed infants in all age groups, but the differences were not statistically significant. The author suggested that in less-developed countries, breast-feeding might not be preferable to artificial feeding. Numerators and denominators in this study were only crudely age adjusted. There is a possibility that clinically important differences could be obscured by these aggregated data as younger children have both the highest mortality and greatest likelihood of being breast-fed. Because mortality risk drops greatly after the first month of life and because breast-feeding would tend to be concentrated early in the "higher-risk" early age period, the use of number of infant-months with a certain feeding method makes age adjustment especially important.

In summary, the majority of studies done in less-developed countries suggest that breast-feeding is associated with lower mortality than is bottle-feeding, at least in certain subpopulations. Although all of these studies have methodologic deficiencies, some of which are serious, the bulk of the evidence appears to support the benefits of breast milk in regard to mortality. In several studies, when the effects of other factors on mortality were taken into consideration, breast-feeding was still shown to be beneficial, although it clearly cannot be concluded to be the sole, or even primary, factor in infant survival.

Two important issues are not well addressed in any of these studies. First, although infectious diseases are the major cause of infant death in less-developed countries, none of these studies directly examined the causes of death in their breast-fed and non-breast-fed populations to determine whether observed associations were diagnosis specific. (The study of Puffer and Serrano,[58] to be discussed under "Gastrointestinal Infections," does look at proportionate mortality due to diarrheal illness.) Including causes of death not related to method of feeding would tend to decrease an investigator's ability to detect an effect of feeding mode upon mortality. Thus, the failure to examine this issue would not negate positive study findings. Second, these studies highlight, but do not resolve, the following questions: (1) If breast-feeding is associated with lower mortality, when is the optimal time and what is the optimal process of weaning? (2) Is there an age when a protective effect of breast-feeding becomes less clinically significant?

Overall Morbidity

"Overall morbidity" is here defined as symptomatic illness noted by the caretaker or leading to a physician's visit or to hospitalization. Morbidity from specific causes of infectious illness is discussed in more detail below. Three studies that look at overall morbidity in less-developed countries are discussed in this section. Morbidity studies in industrialized countries are discussed elsewhere.[39] Several domestic studies that make unique contributions to our understanding of the relationship between feeding method and specific morbidity are discussed below under "Specific Causes of Morbidity and Mortality."

A study assessing hospital admissions was done by the Brazilian Ministry of Education and Culture in Sao Paulo, Brazil.[6] Mothers were interviewed at three maternity clinics in low-income areas of Sao Paulo. Mothers of low-birth-weight or premature infants were excluded; other aspects of study design, selection criteria, and techniques were not described. "Feeding mode" was defined as that used at the time of hospitalization. Few breast-fed infants were included in the study. During an 8-month follow-up period, 42/180 (23.3%) of infants given formula or mixed food at 6 months of age and 0/11 infants who were exclusively breast-fed at 6 months of age were hospitalized. This difference was not statistically significant ($P > .05$*).

Garrett[23] investigated the feeding status and diagnoses of 365 hospitalized Cameroonian children aged 0 to 47 months. Student interviewers questioned the patient's mother about her own age; her husband's occupation; her child's age at the first episode of diarrhea and first bottle-feeding; and number of previous hospitalizations for the child. Twenty percent of mothers were not interviewed, including those who had a child with measles, neonatal tetanus, or, in some cases, meningitis. Feeding mode was that used at the time of hospitalization and was defined as breast milk, bottled milk (largely commercial formula), mixed breast and bottled milk, and "weaned." Distributions of diagnoses were compared for each of these groups. Forty-six percent (64/319) of those who had been breast-fed and 75% (36/48) of those who had been bottle-fed had a primary diagnosis of dehydration ($P < .001$*). Interpretation of this report is limited by the study's hospital-based nature and the failure to control or stratify by the child's age.

In a retrospective cohort study of children born between January 1974 and March 1976 in a Micronesian village, Marshall and Marshall[43] reviewed medical records and interviewed mothers of 49 children who were alive at the time of March 1976 interviews. The rate of hospitalization in the first year of life (or, for those children <1 year old at their interview age) was lowest for those given both breast and supplementary milk formula for that entire period (1/20, 5%), followed by those exclusively breast-fed (1/9, 11%) and those receiving combined breast milk and formula for 6 months, followed by those receiving formula only for 6 months (4/15, 27%). Infants who were exclusively formula-fed had the highest rate of hospitalization (4/5, 80%). Also, the authors, noting that all children hospitalized within 8 weeks of birth had received either supplementary or complete bottle-feeding, suggested that the use of formula might put the very young at great risk. They stated that none of these described differences were statistically significant because of the small cohort number. However, our analysis of the data presented in their table 4 indicates that the difference in hospitalization rates of infants who were exclusively breast-fed and of infants who were exclusively bottle-fed was significant (relative risk [RR] = 7.2, $P = .02$ by Fisher's exact test*).

Young and colleagues,[75] in a cross-sectional study in Tunis, examined the effect of infant-feeding status on the incidence of "severe and moderate" disease at 6, 8, 10, and 12 months of age. They excluded the infectious diseases of childhood, eg, measles or whooping cough; diseases included in their classification were not further defined. Infants were stratified by social class. A statistically significant difference in disease rates between breast-fed infants (1/20) and bottle-fed infants (6/13, $P < .01$; RR = 8.6*) was seen only among the underprivileged children and only at 6 months of age. Mixed and artificial feeding groups were combined as "non-breast-fed," rendering significant differences in disease rates more difficult to detect.

In summary, data from less-developed countries suggest that breast-feeding is associated with relatively lower overall morbidity, especially at younger ages, than is formula-feeding. However, the studies all have important methodologic limitations. No study was as rigorously designed and analyzed as several studies discussed under "Overall Mortality" (above). Overall morbidity results, therefore, need confirmation by further well-designed studies.

Effect of Nutritional Supplementation

Although some research (eg, that of Scrimshaw et al[63]) describes the content of artificial feeding given in certain populations, few studies have examined whether the types or content of artificial feeding given children in less-developed countries affects the children's morbidity and mortality. Below are briefly reviewed those studies that do address this important question.

Watkinson[71] found that, in one West African village, the quantity of breast milk intake at 3 months of age was directly correlated with the age at which traditional supplementary weaning foods were introduced into the diet ($r = .46$, $P < .001$). Watkinson also found that breast milk intake at 3 months of age was greater for eight children without diarrhea-induced weight loss in the first 6 months of life than for 29 children with diarrhea-induced weight loss ($P < .01$). Although traditional weaning foods were not described, the author suggested that one explanation for his findings was that high levels of breast milk intake delayed or decreased the infant's intake of contaminated foodstuffs. He did not examine whether illness or malnutrition was the cause of low levels of breast milk intake in any of his subjects.

In a study discussed under "Overall Mortality," Plank and Milanesi[57] found that infants aged 13 to 38 weeks who were given bottled milk without nonmilk foods had approximately a 70% higher mortality than those given nonmilk supplements in addition to bottled milk. The addition of breast milk did not alter this finding. Although this difference was not statistically significant, the authors suggested that the benefits of adding nonmilk foods outweighed the risks. Another study,[47] also discussed under "Overall Mortality," compared the intake of "milk only," "eggs only," and "other animal proteins," in children who died at 6 months through 3 years of age and a control group matched for sex and month of birth. Other protein intake did not exclude breast milk. Children in the control group more often had "other animal proteins" than did the deceased children (129/143 [90%] *v* 71/136 [52%], odds ratio 8.4*, $P < .001$*). The authors implied that this finding might be attributable either to a direct effect of specific protein sources or to confounding factors related to both mortality and choice of protein source (eg, socioeconomic status).

Wyon and Gordon[74] followed three cohorts of live newborns in rural Punjab for 1 to 3 years, during 1957 through 1959. Diarrhea was the main single cause of death in these groups. The authors found that overall mortality at 6 to 8 months of age was lower for those getting both breast milk and solid foods (0/147) than for those not receiving solid foods (4.5%, 24/531, $P < .02$*). For those aged 9 to 14 months, the death rate was three times greater for those not receiving solid foods; for those aged 15 to 17 months, five times greater, and for those aged 18 to 23 months, ten times greater compared with those receiving both breast milk and solid foods. Each of these differences was stated to be statistically significant, but levels of significance were not provided. The authors found that infants aged 12 to 18 months receiving solid foods without breast milk had a higher mortality than those receiving both solid foods and breast milk. This difference was not present for those older than 18 months, suggesting that 18 months might be a reasonable weaning age. The authors did not describe the types of solid foods given, but suggested that their results represent the importance of high-quality protein in infant diets.

In summary, most of these studies suggest that solid and nonmilk liquid food supplementation to breast-feeding can have significant positive effects upon infant morbidity and mortality. At least two critical questions remain unanswered: (1) What are the optimal weaning foods for different areas and cultures? (2) What is the optimal schedule for adding these weaning foods to the infant diet?

Specific Causes of Morbidity and Mortality

Gastrointestinal Infections

GENERAL. The relation between method of feeding and gastrointestinal illness has been extensively studied. This is especially true for less-developed countries, where gastrointestinal illness is a major cause of morbidity and mortality. The majority of these studies found that breast-feeding was associated with lower rates of diarrhea, but all have the study design limitations discussed in the introduction to this section.

In 13 Latin American study areas, Puffer and Serrano[58] reported proportionate mortality among infants who died between 28 days and 5 months of life. Infants were divided into four breast-feeding categories: (1) breast-fed and never weaned, (2) breast-fed for 1 month or more, (3) breast-fed for less than 1 month, and (4) never breast-fed. The overall proportionate mortality from diarrheal diseases was lower among breast-fed infants who were never weaned (32%; 446/1,405) than among the next three groups (51%, 1,175/2,286; 54%, 1,292/2,384; 52%, 991/1,916, respectively). Proportionate mortalities for groups 2 through 4 did not differ statistically from each other. Findings varied from one Latin American project to another; however, in 11 of 13 projects, the proportionate mortality for the breast-fed infants who were never weaned was lower than that for infants breast-fed for less than 1 month and for those never breast-fed. Although these data suggest that breast-feeding is less often associated with diarrhea mortality than non-breast-feeding, a measurement of proportionate mortality may not be adequate for measuring protectiveness, as the proportion of deaths caused by gastrointestinal illness can vary because of differences in rates for other causes of death as well as differences in rates for gastrointestinal illness. Finally, these data also suggest that a past history of breast-feeding or a recent history of partial breast-feeding in infants currently not breast-fed did not provide protection from diarrhea-related mortality.

Urrutia et al[70] studied morbidity in 417 newborns from Guatemala City and found that the incidence per 100 child-weeks of neonatal diarrhea for artificially fed infants was 2.5 times that for the breast-fed infants (4.8 *v* 1.9, $P < .001^*$). Method of case selection was not given; feeding modes and diarrhea were not defined.

Chandra[10] prospectively studied 70 infants from rural India for their first year of life and compared infants bottle-fed from the first week of life (n = 35) with infants exclusively breast-fed for at least the first 2 months of life (n = 35). Whether bottle-feeding was exclusive was unclear. Groups were matched for socioeconomic status, parental education and occupation, and family size. "Diarrhea" was defined as three or more bowel movements per 48 hours. Bottle-fed infants had three times* the incidence of diarrhea (211 episodes among 35 infants *v* 70 episodes among 35 infants, $P < .001$) and 4.7* times the incidence of medically diagnosed dehydration that breast-fed infants had (14 episodes among 35 infants *v* three episodes among 35 infants, $P < .001$).

In a study in Rwanda, Lepage et al[41] studied 2,339 hospitalized infants less than 2 years old and found a significantly lower mortality in patients with clinically diagnosed diarrhea who had been breast-fed on the date of hospitalization, compared with patients fed formula on the date of hospitalization (6.6% *v* 22.0%, $P < .001$). They did not examine reasons for discontinuing breast-feeding (eg, illness) or relative clinical status at the time of admission.

In a previously discussed prospective study in 11 rural villages of northern India, Scrimshaw et al[63] found the incidence of diarrhea in 0- to 11-month-old infants fed solid foods and nonhuman milk (240/430, 55.8%) to be 1.6 times* that of breast-fed infants (415/1,191, 34.8%; $P < .001^*$). The incidence increased progressively from the breast-fed group, to those fed solid foods without milk supplements (19/50, 38%), to those fed both breast and other milk (487/1,057, 46%), to those fed other milk and solid foods (240/430, 56%). Whether the diarrhea was of infectious origin was not determined, nor was nutritional status compared for feeding groups, although many artificially fed infants were described as "weak."

Also in India, Mittal et al[49] examined feeding patterns among 148 hospitalized infants with diarrhea and among 35 hospitalized control subjects (without diarrhea) who were matched for age and socioeconomic status. Diagnoses of control infants were not described. Differentiation of exclusive breast-feeding from mixed feeding status was not clearly made nor was diarrhea defined. Breast-feeding was less frequent among "cases" (59/148) than among control infants (22/35, odds ratio 2.6*, $P < .005$). The effect was most pronounced among infants less than 7 months old (34/60 cases *v* 15/17 control infants; odds ratio 5.7*, $P < .005^*$).

In Kingston, Jamaica, Grantham-McGregor and Back[27] prospectively followed a clinic cohort of 300 infants, born from March 1967 to June 1968, from birth to 1 year of age. Infants in mixed-feeding programs were treated as bottle-fed, which would tend to minimize chances of finding an apparent protective effect of breast-feeding. The type of formula or supplemental foods used was not described. Reasons for bottle-feeding were discussed in depth. Data were collected on housing and marital status, but results were not stratified by these parameters. The breast-fed group tended to be of lower socioeconomic status than the bottle-fed group. "Gastroenteritis" was defined as "diarrhea without other infection, with more than three bowel movements per day for more than two days, or associated with clinical illness or vomiting." Months of breast-feeding presumably involved a higher proportion of younger infants than did bottle-feeding months. Therefore, if rates of infection are higher at younger ages, independent of feeding mode, months of breast-feeding may represent periods of relatively higher risk of infection. The results could therefore be biased against finding an effect. As with the authors' feeding-group allocations, this would tend to minimize any protective effect of breast-feeding that was found. The overall incidence of diarrhea was high in this population, but these researchers found a relatively higher incidence of diarrhea per "feeding-month" among the bottle-fed infants than among breast-fed infants (33/754 *v* 2/151) (RR = 3.4*; $P < .01$).

Kanaaneh[37] retrospectively studied 610 healthy full-term children aged 6 to 30 months, seen by him at maternal and child health stations in three Arabic villages in Israel. The rate of hospitalization for gastrointestinal illness in the first 6 months of life was nearly 50 times more for those infants exclusively bottle-fed for more than 3 months (27/109, 24.8%) than for those exclusively breastfed for ≥6 months (1/199, 0.5%; $P < .001$). Furthermore, the rate of hospitalization for gastrointestinal illness in the first 6 months of life increased progressively from those exclusively breast-fed, to those breast-fed for more than 3 months but less than 6 months (1/35, 2.9%), to those receiving mixed feedings for more than 3 months (13/187, 7.0%), to those exclusively bottle-fed for more than 3 months (Table 1). The author did not control for potentially confounding factors, nor did he discuss reasons for formula-feeding; however, he did count multiple hospitalizations of a single child only once and excluded cases of potentially nosocomial diarrheal infections.

Schoub et al[62] studied 37 black infants in South Africa admitted to the hospital with gastroenteritis necessitating intravenous rehydration. Enterotoxigenic bacterial strains were isolated from 15 patients (41%). Only one infant (3%) was exclusively breast-fed; 16% of an unspecified number of control infants (random age-matched children attending a surgical outpatient clinic) were exclusively breast-fed. Statistical testing of this association was not done.

TABLE 1. Incidence of Gastroenteritis in Arabic Infants During First 6 Months of Life by Feeding Experience, Western Galilee, Israel*

Feeding experience	Infants Hospitalized	
	No.	Rate/100
Breast only (N = 199)	1	0.5
Breast only for >3 mo but <6 mo (N = 35)	1	2.9
Mixed (breast and bottle) for >3 mo (N = 187)	13	7.0
Bottle only for >3 mo (N = 109)	27	24.8

* Data from Kanaaneh.[37]

Clavano[13] studied 9,622 infants delivered at a large hospital in the Philippines from January 1973 to April 1977 and for whom hospital feeding records were available. During the later part of this time (period II, April 1975 to April 1977), breast-feeding and rooming-in policies were revised in the nursery, and the postnatal period during which infants were not fed was shortened considerably. During period I (n = 4,590 births with known feeding mode), 41.6% were breast-fed, 50.4% were exclusively formula-fed, and 8.0% received mixed feedings. During period II (n = 5,032), the corresponding percentages were 89.4, 5.7, and 4.9. Reasons for feeding choices were not discussed. Although the overall percentage of infants who had low birth weight and were small for gestational age was presented, their allocation among the groups was not specified. Mortality from diarrhea (defined as "too frequent" passage of watery stools or recurrent or protracted watery stools) among infants given breast-feeding, mixed-feeding, and formula-feeding were 0%, 0%, and 0.5%, respectively ($P < .001$ for breast-fed *v* formula-fed*). Among infants in all feeding groups, morbidity from diarrhea was markedly lower* during period II (when the period of postpartum "starvation" was shortened) (Table 2). Diarrheal illness rates among infants given breastfeeding, mixed-feeding, and bottlefeeding for the entire period studied by Clavano were 0.9/1,000, 13/1,000, and 48/1,000, respectively (RR = 50.9*).

However, when data were standardized to adjust for the lower overall morbidity during the period of predominant breast-feeding, the relative risk of diarrheal illness among bottle-fed infants was 20.7.[53]

One study[16] in Malaysia showed no effect of method of feeding on the clinical diagnosis of diarrhea. Sampling technique was nonrandom, and inclusion criteria excluded 87% of the infants in this population (sample: n = 2,000, study; n = 250). Infants were included only if they met the following relatively strict criteria: (1) the first visit to the clinic was before 6 weeks of age, the last visit was after the age of 40 weeks, and the total number of visits was at least 12; (2) the birth weight was at least 2.5 kg or more; (3) there was no record of "nonmilk" supplementary feeds before the age of 40 weeks; and (4) the record information was complete. The "breast-feeding" group included infants

TABLE 2. Diarrheal Illness Among Newborn Infants by Feeding Mode and Data of Birth, Baguio, Philippines, January 1973 through April 1977*

Feeding Mode	Period I Jan 1973–March 1975			Period II April 1975–April 1977			Periods I and II Jan 1973–April 1977		
	No.	Ill	Rate/1,000	No.	Ill	Rate/1,000	No.	Ill	Rate/1,000
Breast	1,910	3	1.57	4,498	3	0.67	6,408	6	0.94
Mixed (breast & bottle)	366	6	13.66	245	2	8.16	611	8	13.09
Formula	2,314	121	52.29	289	3	10.38	2,603	124	47.64
All	4,590	130	28.30	5,032	8	1.59	9,622	138	14.34
Relative risk†			33.3			15.6			50.9

* Data from Clavano.[13]
† Formula *v* breast.

receiving mixed feedings (breast milk and formula), a classification that could minimize differences between breast-fed and bottle-fed groups. Feeding classification was not necessarily based on the method of feeding used at the time of illness. Rather, the author compared rates of diarrhea in the first year of life for infants weaned at various age groupings. A multifactorial analysis examined the independent effects of several factors, including ethnic group, number of children, income, and mode of feeding. Presented data were analyzed bivariately. No significant difference was found in the incidence of diarrhea between feeding groups by either analysis.

In summary, most studies of populations from less-developed countries suggest that breast-feeding is associated with a lower incidence of diarrhea than is artificial feeding. These investigations tend to share a number of limitations, including failure to determine whether reasons for formula-feeding might have been related to a higher initial risk and failure to verify in the laboratory that diarrhea was infectious in origin. Reasons for bottle-feeding were infrequently provided. However, several studies did control for some important potentially confounding variables (eg, socioeconomic status). Furthermore, one study[37] found differences between feeding groups that were so large that they would be difficult to explain on the basis of confounding or of study design limitations alone.

SPECIFIC PATHOGENS. Although this report concentrates on studies from less-developed countries, as mentioned previously, studies from developed countries will be reviewed briefly when they provide special insight into the effects of breast milk on infectious morbidity and mortality. This situation occurs predominantly for studies dealing with specific pathogens.

Salmonella. France et al[21] reviewed the histories of 253 infants less than 1 year of age who had had *Salmonella* organisms isolated from their stool specimens. Five percent (12/253) of these had ever been breast-fed, only one infant had been breast-fed near the time of infection, compared with 27% of an age-matched control population from similar clinical settings ($P < .001$). These researchers looked at neutrophils and macrophages in the breast milk, colostrum, and serum of 60 healthy, lactating mothers. Cells in colostrum or breast milk appeared to be activated against *Salmonella* organisms; they phagocytized and killed more *Salmonella* organisms than did blood neutrophils and did not respond to serum complement. These data strongly support the concept of a primary protective effect of breast milk and of its immunity against *Salmonella* organisms. Additional data on *Salmonella* antibody levels of infants, and on cellular activity and antibody levels in breast-feeding mothers of infants with stool cultures positive for *Salmonella*, might have provided a useful link between the authors' immunologic findings and their conclusions as to the protective nature of ongoing breast-feeding.

Shigella. Stoll et al[64] studied records of 412 patients with culture-proven *Shigella* diarrhea from a representative sample of all patients seen at Dakha (Bangladesh) Hospital between October 1979 and February 1980. Allocation of partially breast-fed children was not defined. Infants less than 2 years old with infections due to *Shigella* organisms (n = 155) were less frequently breast-fed than were infants less than 2 years old whose illness had another cause (59% *v* 78%, $P < .05$). No similar relationship to breast-feeding was found for any other enteric pathogen. The 92 breast-fed children less than 2 years old with *Shigella* diarrhea had milder illness than the 63 non-breast-fed infants: fewer required intravenous therapy (16% *v* 38%, $P < .01$), fewer were admitted as inpatients (5% *v* 19%, $P < .01$), and fewer were less than 80% of weight-for-height standard (34% *v* 48%, $P < .01$). Within the less than 2-year-old age group, age stratification was not done. Allowing for the limitations of a hospital-based study, these results suggest that *Shigella* diarrhea in breast-fed infants may be milder than in the non-breast-fed infants.

Vibrio cholerae. Gunn et al,[28] in an age- and residence-matched pair (case-control) analysis of 61 culture-confirmed, apparently symptomatic, patients with cholera who were less than 1 year of age in Bahrain, selected asymptomatic control subjects from households having a member with culture-proven cholera. Interviews were completed on 42 matched pairs. Significantly more cases than control subjects were principally bottle-fed (RR = 9.0, $P = .0004$). The authors could not determine whether this difference was attributable to a protective effect of breast milk or to contaminated artificial feeding bottles.

In another hospital-based study (hospital catchment probably made this study also population-based) in Bangladesh, Glass et al[24] prospectively looked at 93 mother-child pairs; for each, *V. cholerae* had been diagnosed in another member of the household in the previous 24 hours. Patients were treated with either outpatient oral rehydration or hospitalization. The study was limited to pairs that included mothers without diarrhea and breast-feeding children less than 30 months old. Breast milk was sampled on the day each mother began participation in the study and stools were cultured daily. A diagnosis of cholera in this cohort was based on stool culture; disease was considered clinically significant when the infant had three or more watery bowel movements or four or more loose bowel movements in 48 hours. Thirty children were infected; 63 were not. Presence or absence of infection was not correlated with the proportion of breast milk immunoglobulin A (IgA) that was specific for cholera toxin or for lipopolysaccharide. However, the 19 children who developed clinically symptomatic disease had ingested breast milk with significantly lower titers of antibodies to cholera toxin and lipopolysaccharide ($P < .01$) than did children with asymptomatic infections. The authors did not look at total intake of specific IgA, concentration of specific IgA, or avidity of these antibodies. The authors also did not control for the age of the child, nor did they examine whether breast-feeding might alter the length of infection or symptomatic illness.

To summarize, both of the *V cholerae* studies reviewed above have relatively strong study designs. The first study strongly suggests that breast-feeding is associated with a lower incidence of cholera than is bottle-feeding. The second study suggests that breast milk IgA cholera antibodies may protect the breast-feeding child against symptomatic illness, if not colonization.

Escherichia coli. Surjono et al[65] found 72% (38/53) of their samples of bottle milk from four Indonesian clinics contaminated with aerobic organisms (>10^5 bacteria per milliliter), predominantly with nonenteropathogenic serotypes of *E. coli.* Tests for enterotoxin were not done. Mata and Urrutia[45] studied 81 infants in Guatemala for up to 3 years. They found an increasing number of *E. coli* organisms in the children's stools after weaning and a lower incidence of *E. coli* stool colonization and of symptoms associated with enteropathic *E. coli* in breast-fed infants than in bottle-fed ones. Rowland et al[61] looked at the bacteriostatic properties against *E. coli* of Gambian mothers' breast milk and found that the percentage of time infants were ill with diarrhea was inversely related to breast milk activity against *E coli.* These results did not reach statistical significance, however. Holmgren et al[34] examined breast milk samples from 20 undernourished, breast-feeding Pakistani mothers and found that all had IgG and secretory IgA neutralizing antibody directed at *E coli* toxin. The authors did not attempt to link this finding to symptoms in offspring.

To summarize, one physiologic basis for clinical protection against toxigenic *E coli* diarrhea (*E coli*-specific antibody) has been characterized, but this factor has not yet been associated with the prevention of disease in infants.

Rotavirus. Rotavirus is the most common cause of diarrhea in infants and children less than 3 years of age.[14] The potential protectiveness of breast milk against rotavirus infection has become an extremely popular topic of research. Studies from both developed and less-developed countries are reviewed briefly here.

McLean and Holmes[48] found anti-rotavirus IgA in colostrum at parturition. As is true for many antibodies, levels became quite low by day 3 or 4. Serum antibody levels showed little relationship to levels in colostrum. In a prospective cohort study, Gurwith et al[29] found that 55% (16/29) of non-breast-fed infants and 39% (29/75) of breast-fed infants had rotavirus-positive diarrhea. This difference was not statistically significant. They did not attempt to correlate rotavirus type-specific breast milk antibody or cellular activity with the presence or absence of rotavirus infection in infants.

Weinberg et al[72] presented data from a group of infants with rotavirus infection who were less than 1 year of age. Although the authors stated that breast-feeding offered no protection against rotavirus infection, fewer infants who were currently breast-feeding (n = 7) experienced vomiting than did exclusively formula-fed infants (n = 18) ($P = .027$*, Fisher's exact test). No differences in frequency or duration of diarrhea were found.

Banatvala et al[1] investigated mild or asymptomatic rotavirus diarrhea in a London newborn nursery. They found less infection and shorter virus excretion in breast-fed infants than in bottle-fed infants (RR = 2.6*, $P < .001$). Rotavirus particles were fewer in number and clumped in the stools of breast-fed infants. The same group of researchers[69] later looked at rotavirus type 2-specific IgG and IgA antibody titers in the breast milk of breast-feeding and of non-breast-feeding mothers and found no relationship between antibody titers and infant illness. They did not appear to separate results for breast-fed infants and non-breast-fed infants, nor did they examine anti-rotavirus cellular activity in breast milk. Crewe and Murphy[14] tested daily (for 1 month) 40 newborn infants who were shown to be excreting rotavirus within a few days of birth. Excretion was short-lived and did not appear to confer lasting immunity, as measured by following antibody levels at 8 to 18 months of age. Infection rates did not differ for breast-fed infants and bottle-fed infants and showed no relationship to maternally acquired antibody titers in the infants' serum.

In summary, none of these studies clearly showed that breast milk had a protective effect against symptomatic rotavirus infection, although there was a suggestion that illness may be milder among currently breast-fed infants. The role of breast milk antibody in this regard remains problematic. Future studies attempting to determine its role should ensure that (1) antibody testing is specific for rotavirus, (2) symptomatic rotavirus-positive diarrhea is correlated to type-specific antibody titers in breast-feeding mothers, and (3) the role of the cellular components of breast milk is also determined.

Hepatitis B. Beasley et al[3] examined 147 babies born to asymptomatic carriers of hepatitis B surface antigen (HB_sAg). Sera were examined at 2 to 3 months and at 11 months of age. A slightly lower proportion of breast-fed infants than non-breast-fed infants had sera positive for HB_sAg (49% *v* 53%, not significant) or antibody to HB_sAg (4% *v* 7%, not significant). Breast milk samples from 32 breast-feeding mothers were tested for antigen and antibody to HB_sAg. All were negative. These results suggest that breast-fed infants are at no higher risk than non-breast-fed infants of having sera positive for HB_sAg. The risk of acquiring hepatitis is high for any infant of an HB_sAg carrier; however, breast-feeding does not appear to be contraindicated in a HB_sAg-positive mother who is the caretaker of her own infant.[9]

Khan et al[38] examined the occurrence of stool positivity for hookworm and *Ascaris* ova among 142 children of low-income families in Dhaka. Infants who were exclusively breast-fed (n = 44), although socioeconomically comparable to those given breast milk with supplements (n = 98), were younger. No differences in the rates of excretion of hookworm ova were found between the two groups. The prevalence of *Ascaris* ova among infants less than 6 months old who were exclusively breast-fed (0/23) was lower than the prevalence among infants less than 6 months old who were given supplements (3/14, $P < .01$ by χ^2, $P = .047$* by Fisher's exact test). *Ascaris* ova rates in older children (aged 6 to 24 months) were similar in the two groups, suggesting that the initial protection from infection provided by avoidance of foodstuffs wanes as children age.

Respiratory Infections

GENERAL. The results of studies concerning respiratory infections and method of infant feeding have been mixed. Studies in developed countries were reviewed in a companion report.[39]

Three studies in less-developed countries suggest that breast-feeding protects against respiratory infection. Those were reviewed, as were some that failed to detect such a protective effect.

In a previously discussed hospital-based study in Rwanda, Lepage et al[41] found that case fatality rates were higher for bottle-fed patients less than 2 years old with lower respiratory infections than for those who were breast-fed (39/142, 27.4% *v* 42/313, 13.4%; RR = 2.0*; $P < .001$).

Elliott[18] reviewed chest roentgenograms done on 633 (29.5%) of all 2,143 preschool children in Rarotonga in 1970. Two hundred thirty-two (37% of those reviewed) had radiologic abnormalities. Breast-feeding history was considered positive if the child was being breast-fed during the time period when roentgenograms were taken. Children receiving mixed feeding were apparently included in the breast-fed group. Abnormal roentgenographic findings were seen in 15/82 (18.3%) infants less than 1 year of age, including 4/44 (9.1%) who were breast-fed and 11/38 (28.9%) who were not breast-fed (RR = 3.2,* $P = .021$ by Fisher's exact test*; $P < .05$ by χ^2 testing). The abnormality rate among all preschool children did not vary with their ethnic group, a category considered to be a surrogate for socioeconomic status. Elliott did not compare age-specific radiologic abnormality rates between breast-fed infants and non-breast-fed infants and correctly noted that his data on breast-feeding could thereby reflect the age-relatedness of abnormalities, rather than an effect of breast-feeding.

In a prospective study of rural Indian newborns (see "Gastrointestinal Infections"), Chandra[10] found that the rate of respiratory infection in the first year of life was 1.9 times* higher in infants who were bottle-fed from the first week of life than in infants who were exclusively breast-fed for at least the first 2 months of life. Chandra defined "respiratory infection" as "a cough for ≥72 hours, with or without fever or coryza." Mild symptoms of allergic or other noninfectious origin were therefore probably included. Thus, although he found significant differences between breast-fed infants and formula-fed infants with regard to respiratory symptoms, it is unclear how many of these episodes were infectious in origin. However, he also found a four times* higher incidence of radiologically diagnosed pneumonia in the first year of life for bottle-fed infants compared with breast-fed infants (8/35 v 2/35, $P < .001$ χ^2, $P = .042$ by Fisher's exact test*). This suggests that breast-feeding had a significant effect on the incidence of infectious lower respiratory tract disease.

Several studies suggest that breast-feeding may not protect against respiratory infections. Two of these studies[19,20] are discussed in the domestic portion of this report, and two others under "Gastrointestinal Infections." The latter two studies used loose or unspecified diagnostic criteria in research done in Guatemala and Malaysia, respectively. Urrutia et al[70] found no significant difference between breast-fed infants and bottle-fed infants with regard to rates of respiratory infection. Dugdale[16] included mixed feeding (both bottle and breast) in his breast-fed category. As previously mentioned, this categorization would tend to minimize the probability of finding any potentially protective effect of breast milk. Dugdale found slightly fewer respiratory infections in the breast-fed group than in the formula-fed one for up to 30 weeks of age (relative risks from 1.1 to 1.2 for various age groups*). These differences were not statistically significant, however.

In summary, for the general category of respiratory infection, results concerning differences between breast-feeding and bottle-feeding are contradictory. These contradictions are unlikely to be resolved until there have been studies that use strict diagnostic criteria, clearly separate breast-fed and bottle-fed categories, and adequately control for confounding variables. Differentiating episodes of allergic or asthmatic origin from those caused by infection is crucial. None of the reported studies was able to do this.

Finding that breast-feeding does decrease the mortality associated with respiratory infections would be of great importance in countries with high infant mortality. Thus, the study by Lepage et al,[41] suggesting lower mortality in breast-fed infants compared with bottle-fed infants who had lower rspiratory tract disease, could have an impact on developing countries if its results held true on a community-wide basis. As noted by two groups of research investigators in this area,[20,59] appropriate adjustment for confounding factors can change an apparently statistically significant difference to one that is nonsignificant. Thus, conclusions on this topic for the developing world are at best tentative.

SPECIFIC ORGANISMS: Respiratory Syncytial Virus. A major cause of bronchiolitis and pneumonia in early childhood is respiratory syncytial virus (RSV).[11] Because this agent was discussed only generally in the domestic portion of this report, several articles concerning it are reviewed briefly below.

In a British study, Downham et al[15] found that 100% (21/21) of colostrum samples taken within 48 hours of delivery had neutralizing activity to RSV and 86% (18/21) had RSV-specific IgA and IgG antibodies. Toms et al,[68] however, found that although at parturition 16/16 primiparous women secreted RSV-neutralizing inhibitors that were presumed to be antibody, only 25% (4/16) of mothers tested secreted breast milk anti-RSV antibody at 2 to 6 months post partum. Furthermore, only 29% (5/17) of phytohemagglutinin-reactive colostral lymphocyte samples reacted to RSV. Thus, few colostrum or breast milk samples provided specific immune reactivity to RSV at the time of an infant's greatest risk. Both these studies need to be confirmed in other populations.

Two studies in England have examined the relationship between RSV infection and feeding method. In the case-control study mentioned above in this section, Downham et al[15] found that although no patients were breast-feeding at the time of study, infants hospitalized with RSV infections had been breast-fed in the past significantly less often than a control group of clinic patients (8/115, 7% v 46/167, 27%; $P < .0005$). When cases and control subjects were stratified by socioeconomic status, this difference remained but was not statistically significant in the lowest two socioeconomic strata (odds ratio: 2.8*; $.05 < P < .1$). The study was limited in several respects: (1) Cases were slightly younger than control subjects. Because younger infants are more likely to be breast-feeding, this factor would tend to bias the outcome against the finding of any protective effect of breast-feeding. (2) The diagnostic criteria for RSV infection were not stated. (3) How infants receiving mixed feeding (breast/bottle) were allocated was not stated, but they appear to have been included in the breast-fed group. As with the age distributions of cases and control subjects, this would tend to bias against the finding of any protective effect of breast-feeding. Using birth registers, Pullan et al[59] matched 127 children with culture-proven RSV infections with 503 control subjects of the same age and from the same geographic area. With a logistic discriminant analysis, they determined that breast-feeding, apparently at the time of infection, was significantly less common in cases than control subjects. This difference remained significant when a number of potentially confounding factors were included in the analysis. It disappeared when the presence of another child in the room at night, maternal care, and maternal smoking were included in the analysis. However, maternal care and feeding status were found to be closely associated with one another, and when they were the only factors considered in an analysis, breast-feeding retained its significance. On the basis of this finding, the authors concluded that breast-feeding may be an independent factor influencing infection with RSV.

In a study discussed in detail in the domestic portion of this report, Frank et al[22] found that rates of RSV infection in the first 6 months of life were slightly, but not significantly, lower for infants breast-fed ≥3 months (14/39, 36%) than for those who were bottle-fed (20/42, 48%). Problems with this study include the presence of potentially confounding differences between cases and control subjects and the lack of data on feeding method at the time of infection. The authors did not attempt to relate the rates of infection in breast-fed infants to antibody titers in maternal breast milk.

In summary, RSV-specific antibody is initially present in colostrum of many pregnant women, at least those living in some areas of England. It is not known from the described studies how these titers change over time and whether they, in fact, relate to any effects of breast-feeding on RSV infection. Furthermore, it appears that the incidence of RSV infection is dependent upon environmental factors that are closely related to method of infant feeding. This interrelation makes it extremely difficult to determine the effect of breast-feeding. The relationship, if any, between RSV-specific breast milk antibodies and the occurrence of infection needs to be further studied. The results of the Pullan study strongly support the need to include a broad spectrum of potentially confounding variables in any study examining the effects of feeding mode on the incidence of any infection.

Other Viruses. Frank et al[22] looked at rates of infection for breast-fed infants and bottle-fed infants and found no difference in rates of parainfluenza types 1, 2, and 3; influenza A; influenza B; rhinovirus; enteroviruses; adenovirus; *Herpesvirus hominis*; and cytomegalovirus. In addition to the limitations of this study discussed under "Respiratory Syncytial Virus," the numbers of infected infants included in the analysis for many of these organisms were quite small.

Otitis Media

Studies concerning otitis media have been reviewed in the domestic portion of this report. One is briefly mentioned here.

Chandra[10] (see "Gastrointestinal Infections") compared 35 newborn (Asian) Indian infants who were exclusively breast-fed for at least 2 months with 35 control subjects who were bottle-fed from the first week of life. Cases and control subjects were matched for socioeconomic status, parental education and occupation, and family size; methods of case-control selection and allocation were not described. "Otitis" was defined as a "mucopurulent discharge from the external auditory meatus with or without fever." Non-breast-fed infants had 2.5 times* the number of episodes of otitis over a 12-month period, compared with breast-fed infants ($P < .001$). Data were not given about how many infants were actually being breast-fed at the time of their infection; therefore, whether the protective effect of breast-feeding lasted beyond weaning could not be determined.

Urinary Tract Infections

The relationship of type of feeding to the incidence of urinary tract infection has not been studied in less-developed countries and only cursorily studied in developed populations (thus, it was not reviewed in the domestic portion of this report.)

Cheong[12] conducted a retrospective case-control study at a military hospital, including as cases 25 children, aged 6 months through 14 years, who had had *Escherichia coli* urinary tract infections in the previous 2 years. These cases were compared with randomly selected clinic patients in the same age group who had negative findings on urine cultures. Details of how cases and control subjects were matched with regard to age or socioeconomic status were not provided. Of 21 infected patients without uropathy, two (10%) had been breast-fed; 40% (10/25) of control subjects were breast-fed ($P < .01$). A long-term protective effect of breast-feeding on urinary tract infections is difficult to explain physiologically. These results, therefore, need independent confirmation.

Meningitis and Sepsis

Mata et al[44] (see also "Overall Mortality") looked prospectively at infectious diseases occurring in the hospital, after delivery, in 625 infants in rural Costa Rica. The in-hospital rate of sepsis and of sepsis-associated mortality appeared to drop with the initiation of universal breast-feeding. No clear trend over time was seen for meningitis, although the rate was 1.3/1,000 live births in 1976 and 0.1/1,000 live births in 1980. Interpretation of these types of data is difficult because these time trends could be related to totally unrelated environmental changes or to other circumstances occurring at the same time. The authors did not perform statistical testing, and with the data provided, it cannot be done independently.

In the study of Clavano (discussed above), illness rates from "clinical sepsis" during hospitalization among infants given breast-feeding, mixed feeding, and formula-feeding were 0.05%, 1.15%, and 3.38%, respectively ($P < .001$* for formula-feeding *v* breast-feeding, RR = 72*). Rates of mortality from "clinical sepsis" among infants given breast-feeding, mixed-feeding, and formula-feeding were 0.03%, 0.16%, and 2.46%, respectively ($P < .001$* for formula-feeding *v* breast-feeding, RR = 108*).

Haemophilus influenzae Type B Infection

Lum et al[42] used a matched case-control design to study the relationship between breast-feeding and invasive *H influenzae* type B disease in Alaskan Eskimos, a group with a known high incidence of this disease. Invasive *H influenzae* type B disease was defined by a positive blood or CSF culture. A breast-feeding history was positive if the infant was predominantly breast-fed until the time of illness. Ages of the infants were not given. Using control subjects matched for race, age at the time of the patient's illness (susceptibility), and village (exposure and, to some extent, socioeconomic status), they found breast-feeding to be significantly less prevalent among cases (1/19) than among control subjects (18/38) ($P < .005$). Although levels of anticapsular antibody to *H influenzae* type B were similar in sera of Eskimo women and a different group of control subjects, the geometric mean titer of the same antibody in breast milk of Eskimo mothers was approximately three times greater than in control subjects (healthy mothers from California) ($P < .01$). The authors did not examine other potentially confounding factors, eg, the number of children in the household, maternal education, or maternal care. Other methodologic details of this study have not yet been published.

Breast Milk and the High-Risk Neonate

Interest in the potentially protective effect of breast milk for the premature, low-birth-weight, or otherwise high-risk newborn began with clinical reports[40,66,67] suggesting that breast milk might be useful in halting prolonged epidemics of enteropathic *E coli* diarrhea in newborn nurseries and/or in decreasing the morbidity and mortality associated with these outbreaks. A study by Tassovatz and Kotsitch[67] suggested that raw, but not cooked, breast milk was effective. Unfortunately, the groups receiving raw and cooked breast milk were not well matched; the latter contained a higher proportion of premature infants. These authors[67] and Larguia et al[40] showed temporal data strongly suggesting that providing breast milk was associated with the termination of *E coli* outbreaks. No controlled studies have been done, however, and one cannot rule out the possibility of this association's being due to chance.

Other authors attempted to extend this type of research on enteropathic *E coli* diarrhea to diarrhea from other causes and to other sorts of morbidity and mortality. Jayasuriya and Soysa[36] looked at method of feeding, diarrhea, and mortality in three nurseries in Ceylon. Infants weighed between 1,250 and 2,057 g at birth. The breast-fed infants were heavier and more mature than the formula-fed ones, which would tend to inflate any apparent protective effect of breast-feeding. Twenty-three episodes of diarrhea occurred in 93 bottle-fed infants; no episodes occurred in 19 breast-fed infants ($P = .008$, Fisher's exact test*). Similarly, three deaths occurred in the bottle-fed group and none in the breast-fed group ($P = .569$, Fisher's exact test*). Bacterial pathogens were not identified in stool cultures.

In a study done in Mexico, Gutierrez and Fernandez[30] nonrandomly placed 71 premature infants into one of four groups: group I—22 healthy infants, to receive cow's milk; group II—16 healthy infants, to receive colostrum; group III—eight infants with diarrhea, to receive no colostrum; group IV—25 infants with diarrhea, to receive colostrum. The average weight of infants in group II was 366 g less than that of infants in group I, but infants in group II had less diarrhea (12.5%) than those in group I (45.4%). The difference was not statistically significant by the authors' testing, but it was significant ($P = .029$*) by ours (Fisher's exact test). Infants in groups III and IV appeared to be well matched with regard to gestational age and weight. Infants in group IV had less necrotizing enterocolitis (8%) and sepsis (0%) than those in group III (25% with necrotizing enterocolitis; 25% with sepsis, not statistically significant). Thus, despite impressive disease rate differences between groups, the study may have lacked adequate numbers of infants for statistically valid conclusions to be drawn.

In Bombay, India, Patel et al[56] compared 100 low-birth-weight breast-fed infants with 100 similar bottle-fed infants. Infants with congenital anomalies, respiratory distress, or hyperbilirubinemia, or those who died within the first 7 days of life were excluded. The reasons why control mothers did not breast-feed, the diagnostic criteria for infection, and culture results were not provided. Breast-fed infants had a lower incidence of lower respiratory tract infection, gastroenteritis, sepsis, skin infection, and meningitis than did bottle-fed infants, but differences reached significance only for total infections (35% *v* 54%, $P < .01$) and for sepsis (7% *v* 13%, $P < .05$). The rate for sepsis did not reach significance by our independent testing ($\chi^2 = 1.99$, $P < .20$)*. Overall mortality was twice as high in bottle-fed infants (47%) than in breast-fed infants (23%) ($P < .01$).

Three well-designed, randomized, although apparently unblinded, studies were done by Narayanan et al[50-52] in a newborn nursery in New Delhi, India. In the first two studies, high-risk low-birth-weight (<2,000 g) infants were randomly assigned to receive formula or breast milk. The two groups were similar with regard to weight, sex, and age. In the first study, the breast-fed group was formula-fed at night. A higher proportion of infants who were exclusively bottle-fed had some form of infection (24/38 *v* 9/32, relative risk 4.4,* $P < .01$); the greatest relative difference was for septicemia (not statistically significant*).[50] In the second study, the breast-fed group received fresh, raw human milk in the daytime and frozen human milk at night, while the control subjects received only formula.[51] The population total was 62: 31 cases and 31 control subjects (I. Narayanan, personal communication, 1983). This study noted that all formula cultures were negative and that various patient cultures were positive for *E coli*, *Klebsiella*, *Staphylococcus aureus*, or *Serratia* organisms. Again, the formula-fed infants had a higher incidence of infection ($P < .001$), with differences noted for diarrhea ($P = .026$, Fisher's exact test*), pneumonia, septicemia ($P = .012$, Fisher's exact test*), meningitis, and thrush ($P = .026$, Fisher's exact test*). No breast-fed infant and five formula-fed infants died of infections ($P = .026$, Fisher's exact test).

In the third investigation (which appeared to include the neonates from their first investigation), Narayanan et al[52] allocated by random block design 261 low-birth-weight newborn infants to one of four feeding groups: group I was fed only human milk; group II was fed raw human milk for half the day and standard nursery formula for the other half; group III was fed nursery formula around the clock, together with 20 mL of colostrum three times daily; and group IV was fed only nursery formula. The block design helped to match the infants for factors such as birth weight, prolonged labor, prolonged (>24 hours) rupture of membranes, obvious maternal infection, internal examination of the mother by traditional birth attendant, and birth asphyxia. Low birth weight was not specifically defined in this study. There were fewer infections in infants in groups I, II, and III than in infants in group IV ($P < .001$). Differences between groups I, II, and III were not statistically significant at these sample sizes, although no major infections occurred in the group that received only human milk (group I). Mortality was not discussed.

In summary, results of several randomized studies of low-birth-weight neonates strongly suggest that breast milk as a food source is associated with prevention of infection and mortality in this at-risk population.

DISCUSSION

Research from less-developed countries on the relationship between infant feeding mode and morbidity and mortality related to infectious diseases was reviewed. Studies from developed countries that provided additional insight into this issue or offered organism-specific information were also included. Studies that covered overall mortality, overall morbidity, and specific causes of morbidity and mortality were also reviewed.

We gave more weight in our overall assessment and conclusions to those nonexperimental studies that came closest to incorporating the analytic features that are traditionally required to support causal interpretation of epidemiologic associations.[73]

1. Control for possibly confounding factors was an important feature of study design. Statistical techniques may have varied, but credit was given to studies that attempted to compare breast-fed groups and bottle-fed groups in terms of other factors affecting risks of illness or probability of illness detection. These studies were considered more likely to represent real differences between illness rates in breast-fed infants and other non-breast-fed infants.

2. Dose-response effects were an important feature. Studies that provide clear gradations of amount or proportion of breast milk in a diet and which showed a corresponding inverse trend in illness rates increase the plausibility of a causal relationship between breast-feeding and protection from illness.[73] For example, two studies[13,37] (Tables 1 and 2) appear to demonstrate such "dose-response" effects of this relationship.

3. Strength of association was an important feature of study design. The stronger the relationship,

as measured by relative risk or odds ratio, the less likely that uncontrolled biases could explain away the entire association. For example, Kanaaneh[37] found a relative risk of diarrheal illness of nearly 50 when infants who were exclusively bottle-fed were compared with infants who were exclusively breast-fed in the same Arab village. The existence of such a high relative risk is suggestive of an effect, despite the possibility of several potential biases in this study.

4. When possible biases or study weaknesses were not controlled by either design or statistical methods, we tried to determine in which direction the results could be influenced by these biases. When associations were found in the face of biases expected to diminish the ability to detect such associations, the associations were considered valid and perhaps stronger than the study results would indicate. For example, inclusion of infants receiving mixed (both breast and artificial) feeding in either the exclusively breast-fed group or the exclusively bottle-fed group within a study would obviously lessen the likelihood of finding a difference between breast-fed infants and artifically fed infants. If significant differences were found in a study despite this potential bias, we felt that such an association was real.

Research results on several topics support an association between method of infant feeding and infectious diseases. Many of the studies addressing the relationship of overall mortality to feeding type had serious methodologic shortcomings. Furthermore, although it is true that infectious diseases, as a group, are the major cause of infant death in less-developed countries, only Puffer and Serrano[58] examined any specific causes of death in their analysis. However, those studies that were methodologically more rigorous, ie, those that controlled for important confounding variables, still detected a positive association between breast-feeding and infant survival, although they do not suggest that breast-feeding is the sole, or even necessarily the primary, factor in infant survival.

As with overall mortality, studies on diarrheal illness strongly suggest that breast-feeding is inversely associated with disease incidence and severity. In several studies the excess risk for bottle-fed infants was substantial. Data concerning three specific pathogens, *Salmonella*, *Shigella*, and *V cholerae*, give further credence to this conclusion. Studies concerning *E coli* and rotavirus infections neither refute nor support this association.

Study results were highly persuasive that breast milk protects the high-risk (ie, premature or intrauterine growth retarded) newborn. Furthermore, these studies, as well as one of those pertaining to specific pathogens, help resolve an important question—whether breast milk directly protects against infection or merely allows the infant to avoid contact with contaminated food substances. Support for a direct protective effect includes the following: (1) Narayanan et al[51,52] observed fewer infections and lower mortality in breast-fed infants, even though findings were negative when the formula given to control infants was cultured for organisms. (2) France et al[21] showed a lower incidence of *Salmonella* infections in breast-fed infants, compared with formula-fed infants, and also showed that colostrum cells in healthy, lactating women were activated against *Salmonella* organisms. (3) Tassovatz and Kotsitch[67] found that raw, but not cooked, breast milk appeared to be associated with resolution of a nursery *E coli* outbreak.

The data of Narayanan et al were by far the strongest of these and are still in need of independent confirmation.

Some authors have suggested that breast milk protection may be antibody-specific or immune in origin[26,31,32,54]; related to pH and to differential organism growth; or due to special factors or enzymes isolated from human milk.[5,26,55] Conversely, studies documenting bacteriologic contamination of milk, water, diluted formula, and/or weaning foods have been done in less-developed countries.[2,33,60,65] The organisms found were frequently those usually considered to be nonpathogenic, however. Thus although contaminated foodstuffs are sometimes a source of exposure of infants to pathogenic organisms, the relative importance of contaminated foodstuffs compared with other sources of exposure is not yet well defined. This area should be a high priority for future investigation, especially if some forms of food can be shown to be less susceptible to clinically significant contamination than others.

Results concerning three other topics were less conclusive than those discussed above, although the trend in their results was nearly always in the direction of a protective effect of breast-feeding. The studies on overall morbidity (defined as illness, physician visits, or hospitalizations) had serious methodologic shortcomings, but the weight of the evidence suggested that breast-feeding might be associated with lower overall morbidity than is formula-feeding. Results of studies relating method of feeding to respiratory infections were also contradictory, perhaps in part because they did not differenti ͺe allergic from infectious pathology and because tney inadequately examined potentially confounding factors. (In the latter regard, one study[59] of respiratory syncytial virus infections, conducted in a developed country, suggested that feeding status was closely correlated with an important factor related to infection, ie, maternal care. Feeding method did not appear to have a significant effect independent of maternal care, the presence of another child in the room at night, and maternal smoking.) Finally, results of the few studies dealing with the risk of urinary tract infections, meningitis, or sepsis, although suggestive, permitted no firm conclusions to be drawn.

Discussion of the topic of breast-feeding generates strong opinions. This review was an attempt to assess the nature and quality of the scientific evidence. We found that, for several areas, the evidence is sufficiently strong to conclude that breast-feeding has an important positive health effect. For other conditions the evidence is not yet as strong, primarily because two few studies of sufficient methodologic rigor exist to permit firm conclusions.

SUMMARY (Tables 3 and 4)

Conclusions drawn from investigations of the relationship of infant feeding mode to infectious disease outcomes have generally been limited by study design problems, by unstated or imprecise definitions of feeding mode and outcome(s), and by lack of inclusion of associated—and possibly confounding—factors in the analyses. Thus, a clear understanding of the relationship of feeding mode to morbidity and mortality has not yet been reached. Nevertheless, the weight of the evidence from less-developed countries strongly supports an inverse association between breast-feeding and overall mortality, between breast-feeding and diarrheal-related mortality and morbidity, and between breast-feeding and mortality and morbidity in the high-risk newborn. Further studies are needed to characterize more clearly the nature and strength of these relationships.

Conclusions of studies on other aspects of the feeding mode-morbidity and mortality relationship (eg, to respiratory disease, to other systemic infections, etc) are less certain. Results have been suggestive, but conclusions have necessarily been limited by methodologic shortcomings of studies published thus far. Additional well-designed studies are clearly needed in order to clarify the existence of these latter relationships.

Infection and illness occur when environmental factors (eg, water supply, food contamination, crowding, personal hygiene) allow access of pathogenic organisms to a susceptible host. Susceptibility, in turn, is a function of many host factors (eg, portal[s] of entry, prior immunity, nutritional state). Outcome(s) of infections may also depend on several factors such as access to health care, immune status, and nutritional status. Thus, given contact with pathogenic organisms, no single factor determines outcome (mortality and morbidity) in any given situation. Furthermore, the relative importance of a factor will vary with the specific environment and other conditions. Obviously, breast-feeding cannot be expected to prevent all infectious disease morbidity and mortality in less-developed countries. The data do, however, suggest that breast-feeding can contribute to reducing overall infant and child mortality, morbidity and mortality associated with diarrheal illness, and illness or death in the high-risk (low-birth-weight) newborn. Additional well-designed studies are needed to better define the effects of infant-feeding method and of other factors in specific geographic localities.

RECOMMENDATIONS

The evidence linking breast-feeding of children in less-developed countries to protection from mortality and infectious disease is persuasive, although many important questions remain. Some infection-related issues and recommendations are presented in the domestic section of this report.[39] To permit informed decision making by mothers and public health workers, further research is needed in the following critical issues:

1. How much of the protective effect of breast-feeding is direct, ie, ascribable to components of breast milk, and how much is indirect, ie, attributable to avoiding contact with pathogenic organisms?
2. What are the relative degrees of protection conferred by breast-feeding at various ages of infancy? Is there an age beyond which a protective effect is no longer clinically apparent?
3. What are the specific infectious agents against which breast-feeding is protective?
4. Does the protection conferred by breast-feeding persist after breast-feeding ceases? What is the duration of such residual protection, and does it vary by the age when breast-feeding ends or with the foods (solid foods *v* liquid breast milk substitutes) added to the diet?
5. How much of the protection from infection that breast-feeding confers is attributable to better nutritional status among breast-fed infants?
6. What is the relative importance in various settings of bacteriologically contaminated foodstuffs (weaning foods and breast milk substitutes) as vehicles for transmitting infection to infants? Are any of these foodstuffs less likely than others to act as a vehicle in less-developed countries?

TABLE 3. Salient Points of Studies of Infant Feeding and Infection*

Study	Study Population Design	Numbers	Classification of Infant Feeding	Classification of Illness	Outcomes Measured	Findings			Comments
						RR	95% CI	*P*	
Cantrelle (1971) Senegal	Study period 1962–1968; live births 12/62–4/68; retrospective survey; rural, population-based	8,456 live births	Age at weaning; mixed-feedings probably with unweaned; feeding recall period: 1 yr	Parent questionnaire; illness recall: 1 yr	Death	...	...	...	Only 20 live infants weaned at 0–11 months of age
Janowitz (1981) Egypt	Previous full-term live born sibling to infants born 1977–1978; retrospective cohort study; urban, hospital-based	2,907 parous women; 2,903 children	Age at weaning; unclear how mixed-feedings handled; recall period: to last live birth; maximum length of recall unknown	Maternal questionnaires; period of recall: unclear	Death	3.9†	3.1–5.0*	...	Statistical testing is for "never-breast-fed" "ever-breast-fed" infants
Butz (1981) Malaysia	Study period 1976–1977; all live births of interviewed female; retrospective population-based	5,573 live births; 270 deaths in infancy	Age at supplementation or weaning; unclear how mixed-feeding modes handled; recall period: ≤35 yr	Maternal questionnaires; period of recall: ≤35 yr	Death	...	...	...	Authors present coefficients and T statistics for effects of breast-feeding and other variables on mortality
Dugdale (1980) Australia (aboriginal settlement)	Infants born 1953–1972; detailed analysis: infants born 1953, 1958, 1963, 1968, 1972; retrospective (cohort) record review; rural, population-based	270 births and 41 infant deaths for index years; 1,148 births and 189 infant deaths for entire time period; 666 breast-fed months; 2,818 bottle-fed months	Feeding at time of death; unclear how mixed-feeding status handled; length of recall: 0	Sources: hospital, clinic, and settlement administrative offices records; length of recall: 0	Death	(OR) 1.9†	0.6–6.2†	NS	Statistical testing was done with no. of infant months at risk
Brazilian Ministry of Education and Culture (unpublished) Brazil	Study period unclear (probably 1979); retrospective, partially prospective, survey; urban, clinic-based	259 maternal interviews; study completed on 191 children; 8 deaths	Divided into breast, artificial, and combined for nutritional data; defined as "started on bottle-feeding" for morbidity and mortality; unclear how mixed-feedings were handled in these cases; feeding status was defined as that used at time of illness or death; time period for feeding recall unclear, but certainly <8 mo	Source of data unclear; length of recall for illness unclear, but apparently <8 mo	Hospitalization, death	Hospitalization: ... Death: ...		NS† NS†	Details of this study apparently published in Spanish elsewhere; only 259/825 (31%) of women interviewed met sampling criteria; mothers of low-birth-weight or premature infants were excluded; population selected was from low-income maternity clinics in Sao Paulo
Lepage (1981) South Africa	Children hospitalized between 1/77–12/78; retrospective cohort study; urban and rural areas, hospital-based	2,339 hospitalized-children <2 yr old	Defined as breast-fed if on day of admission they were sucking, with or without additional food; length of recall: 0	Source: hospital records; length of recall: 0	Case fatality rates for: Measles Diarrhea ALRD	Measles: 1.5* Diarrhea: 3.3* ALRD: 2.0*	... ...	<.001 <.001 <.001	
Gunn (1979) Bahrain	Study period fall, 1978; retrospective, matched case-control study; urban and rural, clinic-based	42 pairs	Broken down into exclusively breast- or bottle-fed or into principally breast- or bottle-fed (>50% of their intake at 1 wk prior to illness); authors also looked at those weaned	Source: laboratory data; length of recall: 0		Predominantly breast/bottle: 9.0 Exclusively breast/bottle: 7.0 Weaning: ...	... ...	=.0004 =.07 <.02	Cases and controls matched for age and residence; exclusive classifications do not indicate there was no ingestion of other foods or liquids

			from breast; length of recall: 1 wk						
Glass (1982) Bangladesh	Study period 9/80–9/81; prospective cohort study; hospital-based	93 mother/infant pairs	Only breast-fed infants studied; feeding at time of illness; length of recall: 0	Source: laboratory, hospital charts; length of recall: 0	Illness and symptomatic illness	Illness: . . . Symptoms: . . . Anti-LPS: . . . Anti-CT: . . . (Anti-LPS)(Anti-CT)	. . . .	NS <.01 <.02 <.01	Coverage by hospital may have made this population-based; numbers inadequate for controlling for age; study population includes only children <30 mo of age
Dugdale (1971) Malaysia	Study period: 1960, 1963, 1965; retrospective (cohort) sample; urban, clinic-based	250 infants	Used duration of breast-feedings; mixed-feedings were included in breast-fed group; feeding recall period was unclear, but <1 yr	Source: clinic charts; length of recall: 0	Episodes of respiratory or alimentary illnesses during first 40 wk of life, computed as episodes/yr	RI: 1.1–1.2†	. . .	NS	Nonrandom selection, excluding 1,750 infants by described criteria; numbers include 119 Malay and 131 Chinese; those given non-milk supplements at <40 weeks of age were excluded from study
Jayasuriya (1974) Ceylon	Study period unclear; perspective, case-control study; hospital-based	112 infants between 1,250 and 2,057 g birth weight	Infants were given 1 of 3 described formulas or breast milk; feeding recall: 0	Source: hospital charts and laboratory; illness recall: 0	Diarrhea, deaths, and deaths due to infectious diseases	Diarrhea: . . . Deaths: . . . Deaths related to infectious diseases: . . .	. . . .	=.008 (FET)† =.569 (FET)† =.076 (FET)†	Includes 19 exclusively breast-fed and 93 on assorted artificial formulas; 37 of study population were appropriate for gestational age; 75 were small for gestational age; mortality was high for all groups; breast-fed infants were heavier than those in the other 3 groups
Narayanan (1980) India	Study period unclear; perspective control study; urban, hospital-based	70	32 newborns given breast milk in day and formula at night; 38 given only formula; recall length: 0	Source: hospital charts, laboratory; length of recall: 0	Infectious illness	(OR)4.4†	1.6–11.9†	<.01	
Behera (1980) India	Study period: 1973–1977; retrospective record review; hospital-based	200 infants and children with acute diarrhea	Separated into breast-fed, bottle-fed, breast- plus bottle-fed, or solids-fed; appeared to refer to feeding status at time of admission, but this was not clearly stated	Source; hospital charts and laboratory; length of recall: 0		Breast-fed *v* formula-fed: . . .	. . .	NS	This study did not look at incidence of diarrhea in different groups; rather, it looked at percent distribution of bacterial infections for different feeding categories
Marshall (1980) Micronesia	Live births 1/74–3/76; retrospective cohort study; rural, population-based	49 children	Separated into exclusively breast-fed until age 1 yr, breast plus supplementary bottle for 1st yr of life, breast plus supplementary bottle for 1–6 mo, bottle only, and breast-fed exclusively from birth; feeding status recorded for 1st yr of life for those >1 yr old and up to time of medical records search for those <1 yr old; feeding recall: ≤2 yr	Source: parent questionnaires and hospital charts; length of recall: 0	Hospitalizations for >1 day during first year of life	Exclusively breast *v* bottle: Infants <1 yr old: . . . Infants >1 yr old: . . . Total: 7.2†		 =.17 (FET)† =.14 (FET)† =.022 (FET)†	
Gutierrez (1980 Mexico	Infants born and admitted to neonatal unit between 1/74–3/76;	71 premature infants	Infants assigned to 4 feeding groups: cows milk formula, groups 1 and 3; hu-	Newborns divided into healthy newborns—groups 1 and 2 and	Well groups—diarrhea and NEC Diarrhea cases—	Well: Diarrhea: . . . NEC: . . .		 =.029 (FET)† =.099 (FET)†	Group 1, n-22; group 2, n-16; group 3, n-8; group 4, n-25

TABLE 3.—*Continued*

Study	Study Population Design	Numbers	Classification of Infant Feeding	Classification of Illness	Outcomes Measured	Findings				Comments
							RR	95% CI	*P*	
	perspective case-control study; hospital-based		man colostrum-groups 2 and 4; feeding recall: 0	newborns with diarrhea—groups 3 and 4; source: hospital charts; length of recall: 0	NEC and sepsis	Diarrhea cases: NEC: . . . Sepsis: . . .			 =.2 (FET)† =.053 (FET)†	
Garrett (1981) Cameroon	Study period: February-July of an unstated year; retrospective cohort study; urban and rural, hospital-based	365 hospitalized children aged 0-47 mo	Described as breast-fed, mixed-feedings, bottle-fed, or weaned (those receiving neither breast or bottle); appeared to be feeding status at time of hospital admission; feeding recall: 0	Source: hospital charts and parent interviews; illness recall: 0	Diagnosis of hospitalized children	Breast-fed *v* bottle-fed: Dehydration: . . . Malnourished: . . . Previous hospitalizations . . .			 <.001† NS† =.002	89/96 of those in the weaned group had no form of milk in their diet; 23% of hospitalized children were excluded from study because mothers could not be interviewed, including those with measles, neonatal tetanus, and some cases of meningitis; it is unclear what authors were testing when they obtained *P* value = .0002
Elliott (1975) New Zealand Rarotonga	Study period 1971; live births 1966–1971; retrospective cohort study	82 children <1 yr old	Feeding status at time of examination; mixed-feeding not defined or handled	Positive chest roentgenogram	Positive chest roentgenogram		3.18†	. . .	=.021 (FET)†	
Grantham-McGregor (1970) Jamaica	Study period 1967–1968; consecutive live births; prospective cohort study; University Hospital births (Kingston)	300	Maternal history; mixed-feeding defined and discussed; recall: <2 mo	Maternal history with strict definition; recall: <2 mo	Gastroenteritis		3.39†	. . .	<.01	
Goldberg (1982) Brazil	Study period 1980; Rural NE Brazil; retrospective survey of mothers of children 1-12 mo old	3,457	Ever breast-fed or never breast-fed, by mother's definition; recall: >5 yr for up to 30% of respondents	Maternal survey; recall: see feeding	Death		1.72	. . .	<.001	
Kanaaneh (1972) Israel	Study period 1971; Arabic population of Galilee; retrospective cohort study	610	Mixed-feedings were clearly defined and handled; recall period: up to 30 mo	Hospitalization records	Illness		49.3 (bottle: breast)	. . .	<.0001†	
Narayanan (1981) India	Study period 1980; Low-birth-weight infants; randomized clinical trial; nursery in New Delhi	62	Random assignment to 2 groups: breast milk *v* formula; recall period: 0	Physician diagnosis; some cultures; no recall period	Illness and death		6.0†	. . .	<.001	No systemic infections in those fed breast milk
Narayanan (1982) India	Study period unstated; low-birth-weight infants; randomized clinical trial; nursery in New Delhi	261	Random assignment to 1 of 4 feeding groups: exclusive breast milk, exclusive formula, formula and breast milk, formula and colostrum	Physician diagnosis; some cultures; no recall period	Illness and death		5.5†	. . .	<.001	No systemic infections among those fed only breast milk
Patel (1981) India	Study period unstated; low birth weight (<1.81g) in special	200	Artificially fed included only those unable to breast-feed	Physician diagnosis	Illness and death	Mortality-infection: Overall-mortality:	2.0† 2.0† . . .	. . . . . .	<.01 <.01	

	care nursery; Bombay; prospective nonrandom assignment									
Plank (1973) Chile	Study period 1969–1970; retrospective survey 15 rural communities; latest birth within 5 yr	1,712 mothers; 1,283 children	Age at weaning; mixed-feeding clearly defined; recall ≤5 yr	Maternal questionnaire; recall up to 5 yr	Subsequent deaths among those surviving to various ages	at 4 wk at 3 mo at 6 mo	2.1 2.8 2.0	... ...	... <.01 ...	
Puffer (1973) Latin America	Study period 1968–1970; ecologic study of 15 project areas in Latin America; proportionate mortality	5,974 deaths	By maternal history; mixed-feeding not clearly defined; recall period up to 4 mo	Maternal questionnaire; recall period <1 mo	Diarrheal disease and deaths		...	...	<.001*	Proportionate mortality study
Scrimshaw (1968) India	Study period 1955–1959; prospective cohorts study of all children <4 yr until they reach 4 yr	775	By maternal history; only mixed-feeding clearly defined; recall (see illness recall)	Recall: <1 mo for 90%; quarterly home visits for others	Death		7.9†	...	...	Comparability of artificially fed infants to breast-fed infants in question
Urrutia (1980) Guatemala	Study period 1972–1979; observation by home visit until 4 weeks of age; urban infants	417	Unclear how mixed-feeding handled; recall: ≤1 wk	Home visits; recall: ≤1 wk	Diarrhea	Respiratory infection: Diarrhea:	1.2 2.6	... ...	<.001 ...	
Chandra (1980) India	Study period unstated; exclusively breast-fed for ≥2 mo	35 breast-fed 35 bottle-fed	Only exclusively breast-fed and exclusively bottle-fed included; recall ≤2 wk	Recall ≤2 wk; physicians confirmed most illness	Illness	Respiratory infection: Pneumonia: Dehydration: Diarrhea:	1.91 4.00 4.67 3.01	... ...	<.001	
Mata (1981) Costa Rica	Study period 1978–1980; cohort of low-birth-weight infants fed colostrum; historical controls; ecologic data analysis	26,532	Maternal history by survey; nonmilk supplements frequently provided to breast-fed infants	Maternal history (monthly survey)	Death		...	...	...	No. of low-birth-weight infants unknown
McKenzie (1967) Jamaica	Study period 1962–1963; case-control study; cases were 10% sample of all children who died between age 6 mo to 3 yr in Jamaica over 12-mo period; controls were matched for age and sex; but not for parental income, occupation, or education	204 cases 154 controls	Maternal history by survey; some in exclusive breast-fed group may have been partially weaned; recall: up to 21 mo	Death certificate	Breast-feeding duration		OR=1.68 (>6 mo)?		<.05	Only 36% location rate for controls; 72% location rate for cases

* Abbreviations used are: RR, relative risk; CI, confidence interval; OR, odds ratio; ALRD, acute lower respiratory tract disease; FET, Fisher's exact test; NEC, necrotizing enterocolitis; LPS, lipopolysaccharide; CT, cholera toxin; RI, respiratory infection.
† Statistical testing done by the authors of this review, not by the authors of the study.

TABLE 4. Design Aspects of Studies of Infant Feeding and Infection

Study	Feeding Allocation	Consideration of Potentially Confounding Variables*	Study Designing	Comments
Cantrelle (1971)	Maternal choice; reasons for choice not examined	Parity and birth order discussed; results stratified child's age using 3-mo intervals	Population-based house-to-house survey; response and follow-up rates unclear	
Janowitz (1981)	Maternal choice; reasons for choice not discussed	Controlled for maternal education, age, parity, and previous infants' deaths, using a multiregression analysis technique; presented data on mother's urban/rural/slum status	Hospital survey; response and follow-up rates unclear	
Butz (1981)	Maternal choice; reasons for choice unclear	Used logit analysis or linear probability model including maternal education, age, parity, still births, ethnicity, household income, household composition, household density, presence of piped water or toilet in household, preceding birth interval, child's birth order, urban/rural status, child's birth weight, and whether child was born in hospital	Household survey; response and follow-up rates unclear	
Dugdale (1980)	Maternal choice; reasons for choice unclear	Discussed socioeconomic and sanitary situation of settlement	Reports data available for >90% of children born in 5 years selected for detailed study	Adequacy of record keeping on birth and deaths unclear
Brazilian Ministry of Education and Culture (unpublished)	Maternal choice; examined distribution of reasons for non-breast-feeding and for weaning in total study population; also discussed types of non-breast milk and formulas used	Discussed family's socioeconomic status and child's nutritional status, birth weight, and age, although these were not included in morbidity or mortality analyses	Hospital questionnaires; sample criteria excluded 69% of those interviewed; follow-up rate was 77%	
Lepage (1981)	Maternal choice; reasons for choice unclear	Collected data on child's urban/rural status; stratified feeding status by age of child using 6-mo intervals	Hospital-based sample; selection criteria included 86% of all admissions to hospital of children <2 years of age	
Gunn (1979)	Maternal choice; reasons for choice unclear	Cases and controls were matched for age group and urban/rural status; compared cases and controls in regard to type of milk used, source of water, frequency of using boiled water, other food intake, water ingestion, maternal and health care perimeters, sanitary procedures in the home, and antibiotic usage; nutritional status was not assessed, but population was described as having low incidence of malnutrition	Clinic-based; controls were found for 90% of cases; 76% of case-control pairs were interviewed	
Glass (1982)	All infants studied were breast-fed	Literacy status and occupations in source community were discussed	Clinic-based; response rate unclear follow-up rate apparently 100% for final sample	Nonrandom selection
Dugdale (1971)	Maternal choice; reasons for decision unclear	Multifactoral analyses included ethnicity, family income, and family size; all infants were from lower socioeconomic urban families; weight of infant at each clinic visit was recorded, but not used in mor-	Clinic population; selection criteria eliminated 87.5% of main sample	

		bidity analysis; selection criteria specified birth weight was ≥2.5 kg		
Jarasurya (1974)	Somehow assigned to one of 4 feeding groups	Maternal and family confounders not applicable to this study; study population of newborns had a birth weight between 1,250 and 2,057 g	Hospital-based; response rate and follow-up by definition complete	Breast-fed infants were heavier and more mature than non-breast-fed infants
Narayanan (1980)	Randomly assigned to feeding groups	Maternal and family confounding variables not applicable to this study; cases and controls were matched for birth weight and other risk factors	Hospital-based; response and follow-up rates by definition adequate	Despite matching, breast-fed infants had a slightly lower gestational age and birth weight
Bahara (1980)	Maternal choice; reasons for choice unclear	None	Hospital-based; response rate unclear	No controls
Marshall (1980)	Maternal choice; reasons for choice unclear	Discussed socioeconomic status, occupations, and general sanitation of community and discussed general sanitary care and feeding technique used by mothers; stratified by children's ages, using 1- or 2-mo intervals	Household surveys; response rate unclear; follow-up rate apparently 100%	
Guettierrez (1980)	Somehow assigned	Maternal and family confounders not applicable to this study; gestational ages comparable for all groups; group 2 lighter than the other 3 groups; all patients were newborns	Hospital-based; selection criteria unclear; response and follow-up rates by definition 100%	
Garrett (1981)	Maternal choice; mothers' decision on feeding mode was related to other recorded variables; reasons for weaning were also discussed; reasons for artificial feeding and types of artificial feeding were discussed in detail	Data were collected on maternal age, paternal occupation, and child's admission weight, age, no. of hospitalizations, and ethnic group; weights were compared with expected weight for age according to Wellcombe criteria; malnutrition was one diagnosis discussed in paper; noted variables were not used in analyses of morbidity	Retrospective, hospital-based; response rate 80%	
Chandra (1979), India	Maternal choice; reasons not discussed	Groups matched for socioeconomic status, parental education and occupation, and family size	Follow-up complete; hospital-based population; selection could include allergic patients	Individual causes of death not examined
Elliott (1975), New Zealand (Raratonga)	Maternal choice; reasons not discussed	Abnormality rate did not vary with ethnic group (said to be a surrogate for socioeconomic status); age stratification not done	All children on island selected; follow-up apparently complete; no recall	Socioeconomic data collected but not presented; possible correlation with ascariasis
Grantham-McGregor (1970) Jamaica	Maternal choice; reasons discussed and analyzed	Parity and age considered in bivariate analyses	Selected 300 consecutive hospital births; 273 (90.1%) still followed at 1 yr	More nonworking than working mothers breast-fed infants at 6 mo
Goldberg (1982) Brazil	Maternal choice; reasons not discussed	Used linear logistic regression to include urban/rural status, age at last birth, time since last birth, employment status, use of maternal-child health services, education	Selection of mothers for interview not specified	Among non-breast-fed, mortality highest if mother worked

TABLE 4.—*Continued*

Study	Feeding Allocation	Consideration of Potentially Confounding Variables*	Study Designing	Comments
Kanaaneh (1972) Israel	Maternal choice; reasons not discussed	Discussed sanitation, although not by feeding groups	Excluded low-birth-weight infants, twins, and those with congenital anomalies	Multiple hospitalizations for same child counted once
McKenzie (1967) Jamaica	Maternal choice; reasons not discussed	Cases and controls matched for birth month and for sex	Only 72% of cases located; only 56% of controls located	
Narayanan (1981) India	Random selection; group I expressed breast milk, group II nursery formula	Matching by randomized block design to control for prolonged labor, >24 h of leaking or ruptured membranes; obvious maternal infection, internal vaginal examination by traditional birth attendants, birth asphyxia	Hospital-based; follow-up complete	No major infections in breast-fed babies
Narayanan (1982) India	Random selection: I, human milk; II–IV, included formula either alone with breast milk or with colostrum	Matching by randomized block design to control for prolonged labor >4 h rupture of membranes, obvious maternal infection, internal vaginal examination by dais, birth weight, birth asphyxia	Selection criteria included ability to be fed orally and ≥3-d stay; follow-up complete	Design similar to that of Narayanan (1981); overlap uncertain; no systemic infections in exclusively breast-fed infants
Patel (1981) India	Formula-feeding only if mother "could not" breast-feed	Bivariate analysis by birth weight and gestation	Infants with hyperbilirubinemia, respiratory distress, and congenital anomalies excluded; follow-up complete	Some mixed-feeding if quantity of maternal milk inadequate
Plank (1973) Chile	Maternal choice; reason for bottle-feeding collected and discussed	Controlled for maternal age, parity, education, sanitary status	"Complete" (96%) community survey	Mortality among mixed-feeding group only slightly better than among bottle-fed group
Puffer (1973) Latin America	Maternal choice	Ecologic study	All families in project area were included	Findings varied among project areas; past history of breast-feeding did not seem to provide protection
Mata (1981) Costa Rica	Maternal choice	Mortality in breast-fed *v* formula-fed infants not compared	Cohort of all infants born in single hospital; followed monthly; loss to follow-up not discussed	Decrease in hyaline membrane disease also noted in this ecologic study
Scrimshaw (1968) India	Maternal choice; most, if not all, bottle-fed infants associated with "weakness" or maternal death	Seasonality discussed with bivariate analysis	Children of all families in 11 villages included; details of follow-up rates not discussed	
Urrutia (1980) Guatemala	Maternal choice; reasons not discussed	Socioeconomic factors (mother's marital status, education, literacy), access to latrine and to piped water discussed but not controlled for	Method of case selection not given	Most deaths among preterm infants

* Specific confounding variables reviewed included the following: maternal—care, occupation, education, age, parity, smoking; paternal—occupation or education; family—Socioeconomic status, size, sanitation; child—nutrition, birth weight, age. If any of these variables are not mentioned above for a particular study, they were not mentioned or handled in any clear fashion in that study.

RESEARCH CAVEATS FOR MORTALITY AND INFECTION STUDIES

Investigations designed to answer these and related questions will be most beneficial when their study design and presentation are methodologically rigorous and as comprehensive as possible. Investigators in this area can help reassure themselves and interested observers of the validity of their study conclusions by giving careful attention to important details:

1. *The importance of considering potentially confounding factors in study analyses cannot be overemphasized.* Study design and data analysis should take into account the many confounding factors known to be associated with both feeding method and childhood morbidity and mortality. In particular, careful attention to the possibility of bottle-fed infants having become ill prior to their beginning bottle-feeding would be useful. In addition, investigators should make use of opportunities that exist to employ randomized control trials such as those carried out by Narayanan et al.[50-52] This study design allows avoidance of many of the potential biases that confound (and thus complicate) data analyses; investigators (and careful readers) can thus have greater confidence in the validity of the results of such trials.

2. *In reporting their work, investigators should carefully document elements of their study most likely to be affected by bias.* These include selection criteria and techniques, populations and numbers of persons studied, response and follow-up rates, content of all artificial feedings and weaning foods, reasons for using a specific feeding method, clear definitions of feeding mode (including separate analyses of "mixed feeding" groups wherever possible). Microbiologic purity of the water supply used to prepare formula or weaning foods should be documented when possible.

3. *Diagnostic criteria for disease entities should be clearly described* (eg, diarrhea as more than three loose stools per day for at least two days). When feasible, such criteria should include laboratory data and health worker evaluation. Attention to details of disease description will result in more valid estimates of whether protection is conferred by breast-feeding.

4. *Investigators examining outcomes among low-birth-weight infants should separately analyze and present outcomes from premature infants and those who are small for gestational age* as the risk of infections in these two groups may differ.

5. *Infecting microorganisms (as well as negative cultures) should be documented and reported insofar as possible.* Investigators should attempt to link their data on cellular or humoral immunity in breast milk or colostrum samples to outcomes for infants receiving those feedings.

6. *Interactions of other risk factors with feeding method should be examined in detail to determine which infants are at highest risk from artificial feeding in a given environment.* Such examination might lead to suggestions for steps that could be taken to minimize risk for infants who, for practical reasons, cannot be breast-fed.

7. *Techniques used for statistical analyses of study data should be clearly explained.* Investigators should present sufficient raw data to allow the interested reader to replicate at least the univariate analyses.

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