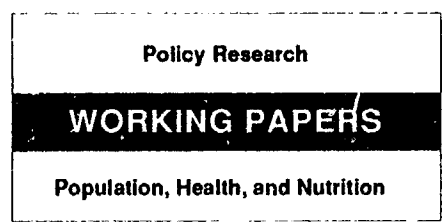


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Population and Human Resources
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Mortality Reductions from Measles and Tetanus Immunization

A Review of the Evidence

Michael Koenig

Tetanus and measles account for more than 2.5 million childhood deaths annually — and immunization programs could significantly reduce those numbers. With tetanus vaccinations, two doses may be necessary.

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In recent years, tetanus and measles are estimated to account for more than 2.5 million childhood deaths annually; measles alone may account for more than 2 million such deaths. Koenig reviews empirical evidence on the most effective and feasible strategies for measles and tetanus vaccination programs.

Koenig found that tetanus and measles immunization programs could significantly reduce deaths among children up to the age of 4 in many developing settings. Vaccinations had a pronounced effect in reducing childhood deaths from measles — with benefits sustained over time, and with the greatest benefits accruing to

the most disadvantaged children. He found little support for the existence of a replacement mortality effect.

Studies on maternal immunization against tetanus showed a great reduction in the number of neonatal deaths, but considerable uncertainty about the number of doses needed and how long the immunity lasted. Recent evidence suggests that giving the mother two doses of tetanus toxoid may confer significant levels of protection against neonatal death from tetanus for 15 years or more. Evidence on the impact of a single dose is less conclusive.

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**Mortality Reductions from Measles and Tetanus Immunization:
A Review of the Evidence***

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* Paper prepared for the Johns Hopkins Institute for International Programs/World Bank Seminar on Child Health Priorities in the 1990s, Baltimore, Maryland, June 20-22, 1991.

In recent years, there has been increased recognition of the paramount importance of tetanus and measles as causes of childhood death in the developing world. It has been estimated that these diseases may together be responsible for more than 2.5 million childhood deaths annually. Considerable debate and uncertainty remains, however, concerning the actual reductions in childhood mortality which would result from the prevention of these diseases through immunization. Equally important, many unresolved questions remain regarding the most cost-effective and feasible operational strategies for measles and tetanus vaccination programs. The objective of this paper is to review existing empirical evidence on tetanus and measles immunization pertaining to these issues.

MEASLES IMMUNIZATION

Measles has been estimated to account annually for as many as two million deaths to children worldwide (WHO, 1985). The risk period for measles begins when protection conferred by maternal antibodies wanes, and continues throughout early childhood. The beginning of the risk period appears to vary considerably between settings and according to residence, with the onset of measles cases frequently reported as early as 4-6 months of life in many urban African settings, but generally later in other settings such as South Asia (Assaad, 1983).

Mortality Impact of Immunization

The main studies which have evaluated the impact of measles immunization upon reductions in childhood mortality are summarized in Table 1. In the following sections, the study design and analytical approaches taken by each of these studies, as well as their principal findings, are reviewed.

The Kasongo study in Zaire represents the earliest attempt to systematically evaluate the impact of measles vaccination upon child survival (The Kasongo Project Team, 1981). All children in one area born during or after September, 1974 were offered measles vaccination at 8 months of age. A total of 255 children in this area accepted measles vaccination during the period of the study, representing 83 percent of all eligible children. Three comparison groups of unvaccinated children were also identified: 1) children born during the same period from a neighboring area where vaccination had not been offered, 2) children from the same area who were born during an earlier period (1973- 1974), and 3) children from the neighboring area also born during this earlier period. Survival status of children was ascertained through a system of quarterly household morbidity and mortality surveillance, carried out from mid-1974 through the end of 1977.

TABLE 1: SUMMARY OF MEASLES VACCINATION STUDIES

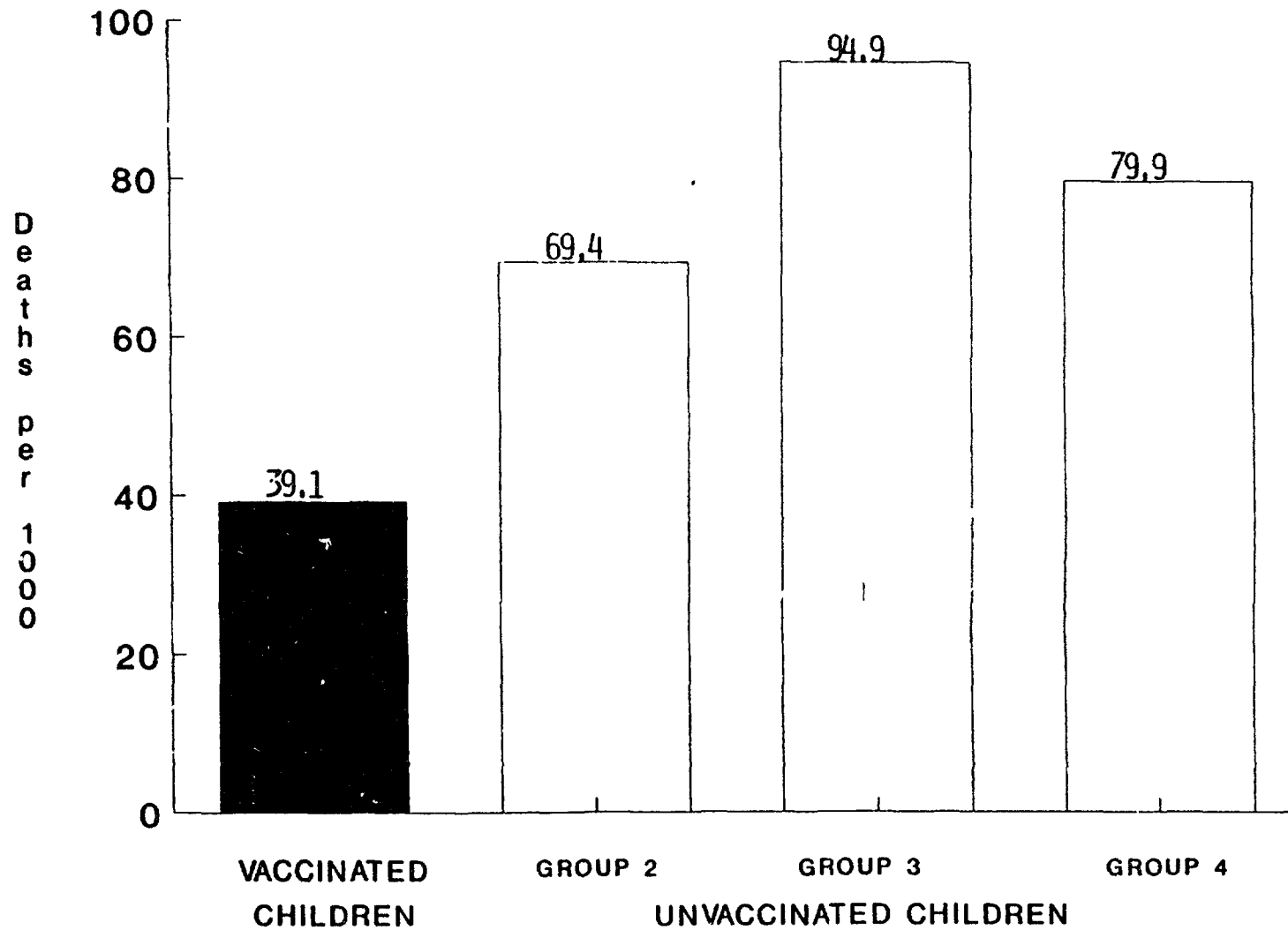
STUDY	LOCATION	STUDY PERIOD	STUDY POPULATION	MAIN FINDINGS
THE KASONGO PROJECT TEAM	ZAIRE	1974-1977	255 VACCINATED CHILDREN 3 CONTROL GROUPS OF UNVACCINATED CHILDREN	30-49% REDUCTION IN 7-35 MONTH MORTALITY
AABY, ET AL.	GUINFA-BISSAU	1980-1981	803 VACCINATED CHILDREN 193 UNVACCINATED CHILDREN	72% REDUCTION IN 6-35 MONTH MORTALITY
GARENNE AND CANTRELLE	SENEGAL	LATE 1960s	NA	31% REDUCTION IN 6 MO. - 3 YR. MORTALITY
CLEMENS, ET AL.	MATLAB, BANGLADESH	1982-1984	536 DEATHS 1072 AGE-SEX MATCHED CONTROLS	36% REDUCTION IN 10-60 MONTH MORTALITY
KOENIG, ET AL.	MATLAB, BANGLADESH	1982-1985	8135 VACCINATED CHILDREN 8135 MATCHED UNVACCINATED CHILDREN	UP TO 46% REDUCTION IN 9-60 MONTH MORTALITY

The mortality experience of these cohorts of children during the age interval 7-35 months was compared using life table techniques. The results of this analysis demonstrated a pronounced impact of measles vaccination upon childhood mortality levels (Figure 1). Mortality among the cohort of vaccinated children was substantially lower than among the three control groups of unvaccinated children: 39 per 1000 vs. 69-95 per 1000 during the age period 7-35 months. This translates into mortality reductions of between 44 to 59 percent among vaccinated children, depending upon the control group chosen. Differences between groups were most marked during ages 7-21 months, the period corresponding to the greatest risk of measles-related mortality.

Two other studies from Africa merit consideration. A study in Guinea-Bissau compared the subsequent one year mortality experience of two groups of vaccinated children in 1980 and 1981 with two groups of children from the same area and periods who did not attend a measles campaign (Aaby, et al. 1984). Although the numbers in the study were comparatively small, especially the number of unvaccinated children (803 vaccinated and 193 unvaccinated children), the results indicated a markedly lower mortality level during the following year among immunized children-- as much as 72 percent lower among children aged 6-35 months. In a second study, Garenne and Cantrelle (1986) analyzed the impact of two measles vaccination campaigns based on data from the Khombole area of Senegal over the 1965-68 period. The subsequent mortality experience of vaccinated children aged 6 months to 10 years in a set of villages selected for a measles vaccination program was compared with a control group of children from other villages where measles vaccination had not been offered. The findings of the study indicated a reduction in mortality among younger vaccinated children (6 months to 3 years) of 31 percent. The reduction in mortality among older children (3-10 years) was more modest (14 percent).

The two other major studies of mortality impact originate from a measles vaccination program in the Matlab study area of the International Centre for Diarrhoeal Disease Research (ICDDR,B) in rural Bangladesh. Since 1966, the ICDDR,B has maintained a system of continuous demographic surveillance in its rural field site in Matlab, consisting of the bi-weekly registration of vital events and periodic censuses. In 1982, the study area consisted of 149 villages with a total population of approximately 180,000. In 1978, half of the study area was designated as an intervention area for an experimental maternal and child health/ family planning program provided by the ICDDR,B; the other half remained a comparison area, with services limited to the less intensive government program. In early 1982, as part of a carefully phased expansion of services, measles vaccination was introduced into two of the four sub-areas of the intervention area (termed blocks); this service was expanded to

FIGURE 1. COMPARISON OF MORTALITY EXPERIENCES OF
VACCINATED AND UNVACCINATED CHILDREN AGED 7-35 MONTHS:
KASONGO, ZAIRE, 1974-77



SOURCE: THE KASONGO PROJECT TEAM, 1981

the remaining two blocks in the fall of 1985. The fact that measles vaccination was introduced in this phased manner makes it possible to evaluate its impact upon subsequent mortality.

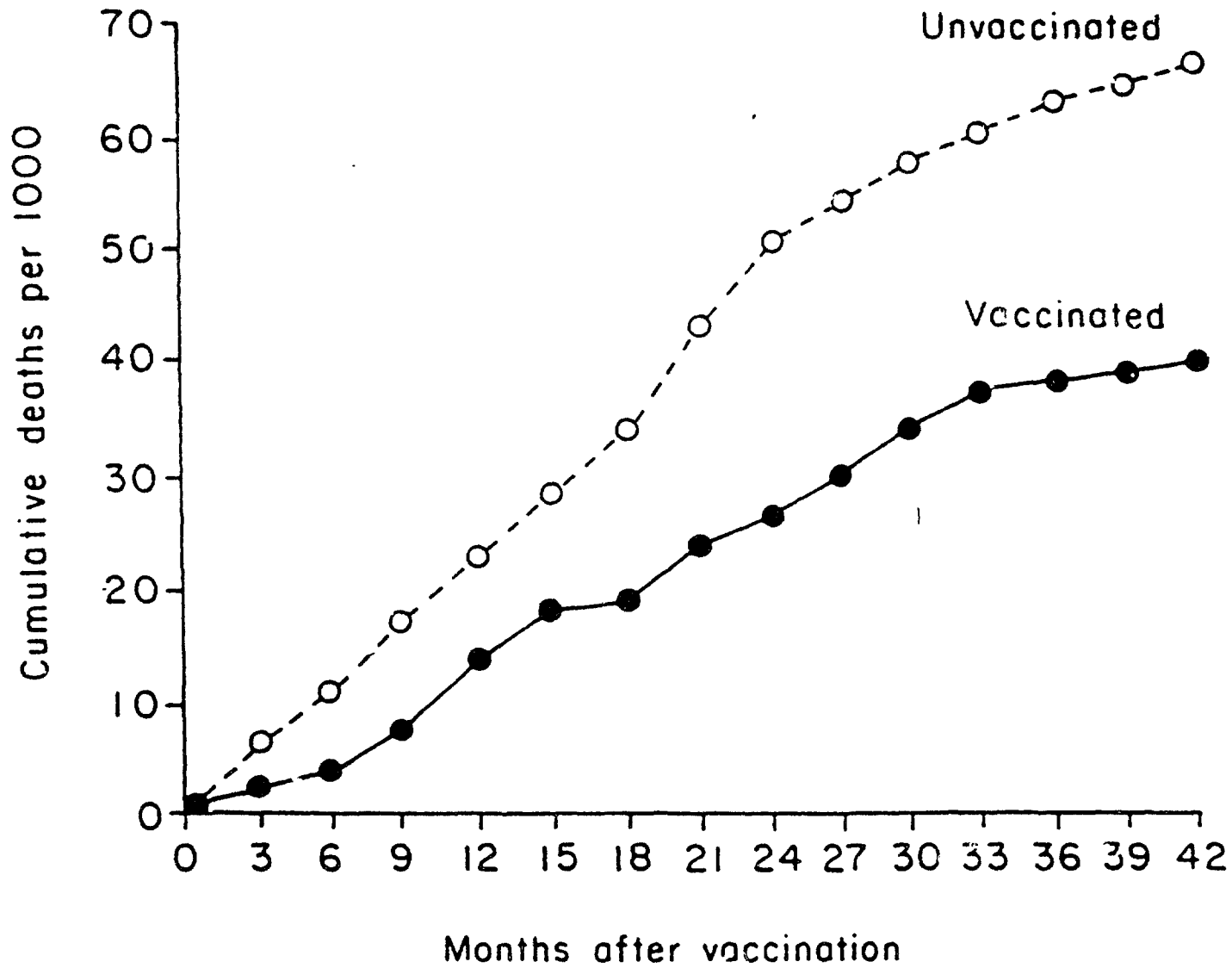
The first evaluation of the impact of the Matlab measles immunization program was a retrospective case-control study consisting of 536 deaths to children aged 10-60 months of age between early 1982 and the end of 1984 (Clemens, et al. 1988). These cases were randomly matched by age and sex with 1072 controls (i.e., children who survived) from the two blocks where vaccination was not offered, and compared in terms of their prior measles immunization status. Measles immunization was found to be associated with a child mortality rate which was 36 percent lower during the study period.

The second study based upon the Matlab measles vaccination program consisted of a longitudinal cohort analysis following children through late 1985 (Koenig, et al. 1990). All 9-60 month children in these two blocks who received measles vaccination during 1982-85 were eligible for inclusion in the study. These children were randomly matched with unvaccinated children of similar age from the other half of the intervention area, resulting in a final analysis cohort of 8135 vaccinated and 8135 unvaccinated children. Through a comparison of the relative mortality experiences of these two cohorts of children from the date of vaccination to the end of the observation (death, out-migration, exceeding five years of age, or the end of the study period, October, 1985), it was possible to evaluate the effect of measles vaccination upon short and longer-term survival. As Figure 2 shows, a striking differential in cumulative mortality risks according to vaccination status was evident. At 42 months from the date of vaccination, vaccinated children experienced mortality risks which were 40 percent lower than their unvaccinated counterparts.

Replacement Mortality

An issue of direct relevance to the impact of measles vaccination programs, but one which remains under considerable debate, is the replacement mortality hypothesis. According to this hypothesis, children 'saved' from death from a specific cause may continue to be at elevated risk of death from other unaddressed causes, resulting in little improvement in overall survival levels. While potentially relevant to many health interventions, this hypothesis has most commonly been applied to the issue of measles and measles immunization (see The Kasongo Project Team, 1981; Mosley, 1985. If substantiated, then the contribution of measles vaccination may be largely to delay rather than prevent childhood mortality, calling into question

FIGURE 2. CUMULATIVE MORTALITY RATES BY MEASLES VACCINATION STATUS: MATLAB INTERVENTION AREA, 1982-85



the efficacy of this intervention as a means for improving child survival. The evidence on measles vaccination and replacement mortality is considered from two different perspectives in the following sections.

Convergence in "Survival Over Time

If replacement mortality was evident, vaccinated children would be expected to experience improved survival in the short-run relative to unvaccinated children, but comparatively higher mortality levels in the longer run, as they would remain highly vulnerable to death from other causes. The result would be a convergence between vaccinated and unvaccinated children in survival probabilities over time.

The authors of the Kasongo study presented evidence which they interpreted as providing support for this hypothesis. Their analysis indicated that while vaccinated children had improved survival chances during the ages 7-21 months, the primary risk period for measles and measles-related mortality, the survival advantage of vaccinated children tended to diminish at later ages (22-35 months). However, as Aaby, et al. (1981) showed in a re-analysis of the Kasongo data, too few deaths occurred in this study population in this older age group to support the authors' original conclusions. Instead, the most salient finding of the study remains the marked reduction in mortality among vaccinated children throughout the entire age span, with reductions ranging from 44 to 59 percent lower among children aged 7-35 months.

The study by Clemens, et al. (1988) in Matlab also considered the issue of replacement mortality in detail. First, the authors examined whether the protective efficacy of measles vaccination for cases and controls selected during the second half of the year-- corresponding to after the measles season in Bangladesh-- might be negative, in contrast to cases and controls selected during or shortly after the primary measles season, when protective efficacy should be positive. The finding of a negative protective efficacy during the period after the measles season would reflect higher replacement mortality among vaccinated children. The results, however, did not provide support for a replacement mortality effect, since the protective efficacy of vaccination was positive and significant during both periods. Second, the authors evaluated whether among cases and controls selected in 1982, there was evidence of a reduction in mortality among vaccinated children in the initial year, followed by higher mortality rates relative to unvaccinated children in the ensuing two years (1983-84). The results provided no evidence of a decline in the effect of measles vaccination with increasing time from vaccination, once again failing to provide evidence of a replacement mortality effect.

Data from the Matlab cohort study by Koenig, et al. (1990) lead to similar conclusions. Among the cohort of children vaccinated at <12 months of age and their matched controls, if replacement mortality were present, one would expect to see higher mortality among vaccinated children with increasing time from vaccination, leading to a partial or complete convergence in survival curves for the two groups. The results instead indicate that vaccinated children continue to experience relatively lower mortality at almost all subsequent age intervals. Moreover, the magnitude of reductions in mortality from measles vaccination reported in these two studies (between 36 and 46 percent) suggest that even if such an effect were present, its impact upon lessening the mortality gains resulting from measles vaccination would be quite minor. The studies from Matlab thus provide no support for the existence of a replacement mortality effect.

Impact Among High-Risk Children

If replacement mortality were present, it should also be expected that the most vulnerable children would benefit least from measles immunization, since it is these children who continue to remain most at risk of death from other unaddressed causes. Within the context of South Asia, high risk children would include females and those from the poorest households, both of which have been shown to experience significantly higher mortality risks during the early childhood period (D'Souza and Chen, 1980; D'Souza and Bhuiya, 1982). Data from the Matlab cohort study on measles immunization permit a more detailed investigation of this hypothesis.

Figure 3 shows life table results of the differential impact of measles vaccination upon mortality according to sex of child. If replacement mortality was present, little difference in the survival curves of female children according to vaccination status would be expected, since they would continue to be at high risk of death from other causes. The results of this figure do not provide support for the replacement mortality hypothesis, and in fact, indicate the opposite-- that female children may benefit more from vaccination in terms of mortality reductions. Vaccinating a female child against measles provides her with roughly the same survival chances as an unvaccinated male child. These results are illustrated in greater detail in Figure 4. Although the relative reductions in mortality are not significantly different for male and female children (36 percent and 41 percent, respectively), because of the much higher mortality levels among female children during this age period, the absolute reduction in mortality for female children is more than twice that for male children (37 deaths vs. 17 deaths per 1,000 live births at 42 months post-vaccination).

FIGURE 3. CUMULATIVE MORTALITY RATES BY MEASLES VACCINATION STATUS AND BY SEX: MATLAB INTERVENTION AREA, 1982-85

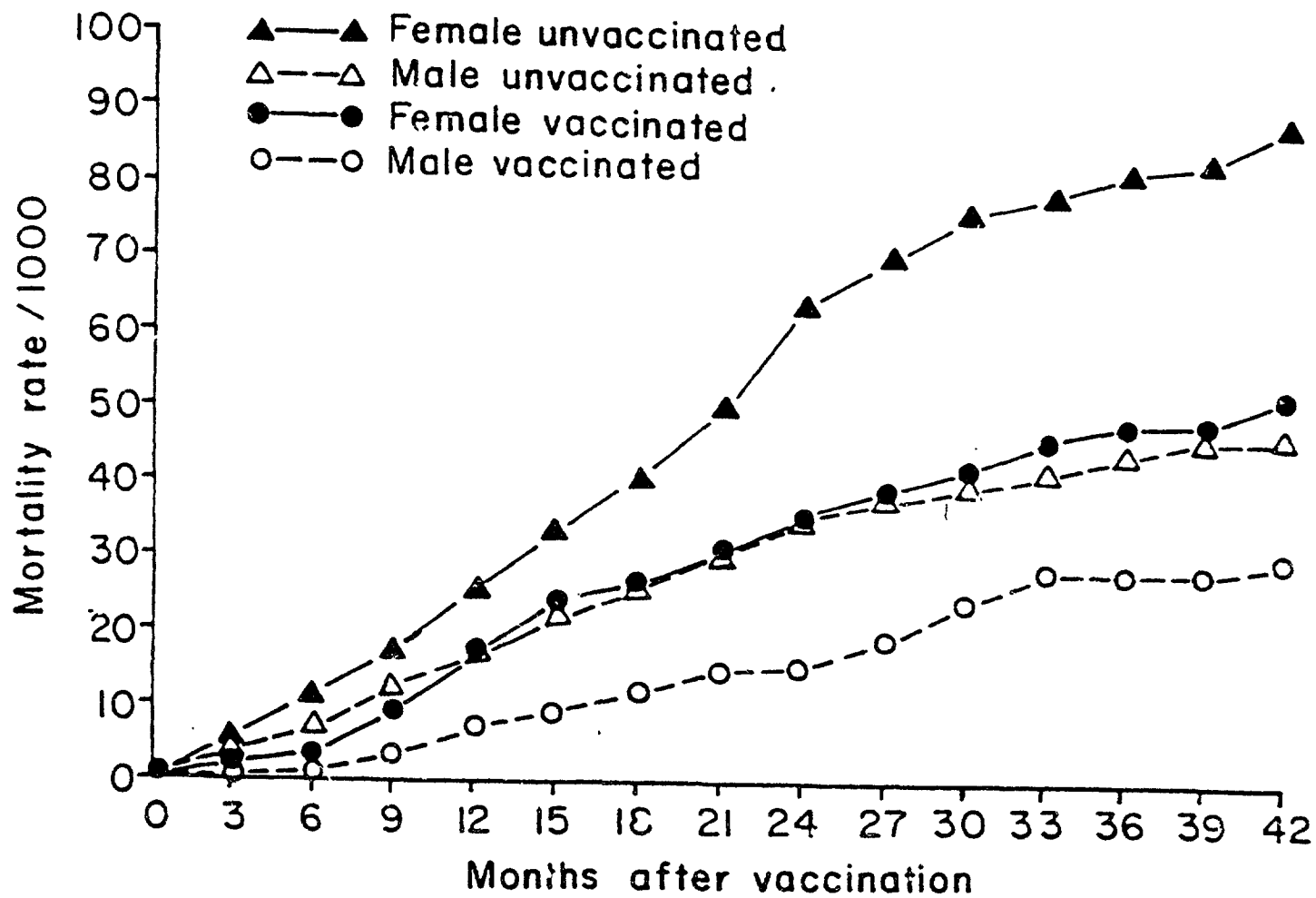
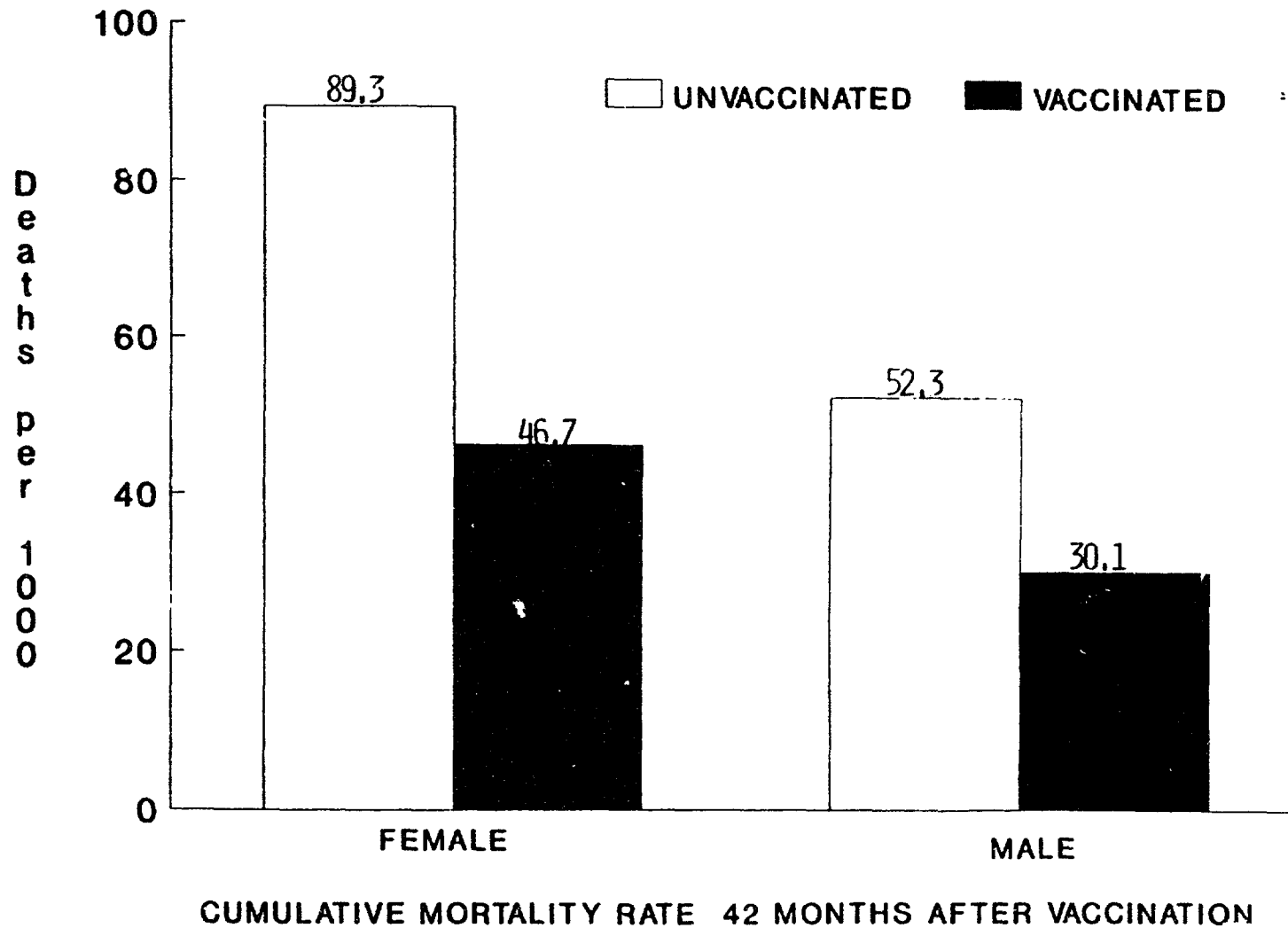


FIGURE 4. EXCESS FEMALE DEATHS BY MEASLES VACCINATION STATUS AMONG 9-60 MONTH CHILDREN: MATLAB INTERVENTION AREA, 1982-85



Similar results are evident in the relationship between measles vaccination, household area, and child mortality, a primary indicator of socioeconomic status among rural Bangladeshi families (Figure 5). While the presence of a child replacement effect would argue in favor of a much weaker effect of vaccination upon child survival among children from the poorest households (area of <200 sq ft), no such association is evident. The results indicate that children of all socioeconomic strata benefit from measles vaccination in terms of lower mortality risks. Although not as pronounced as in the case of sex, children in the poorest households benefit somewhat more from vaccination in terms of absolute reductions in mortality.

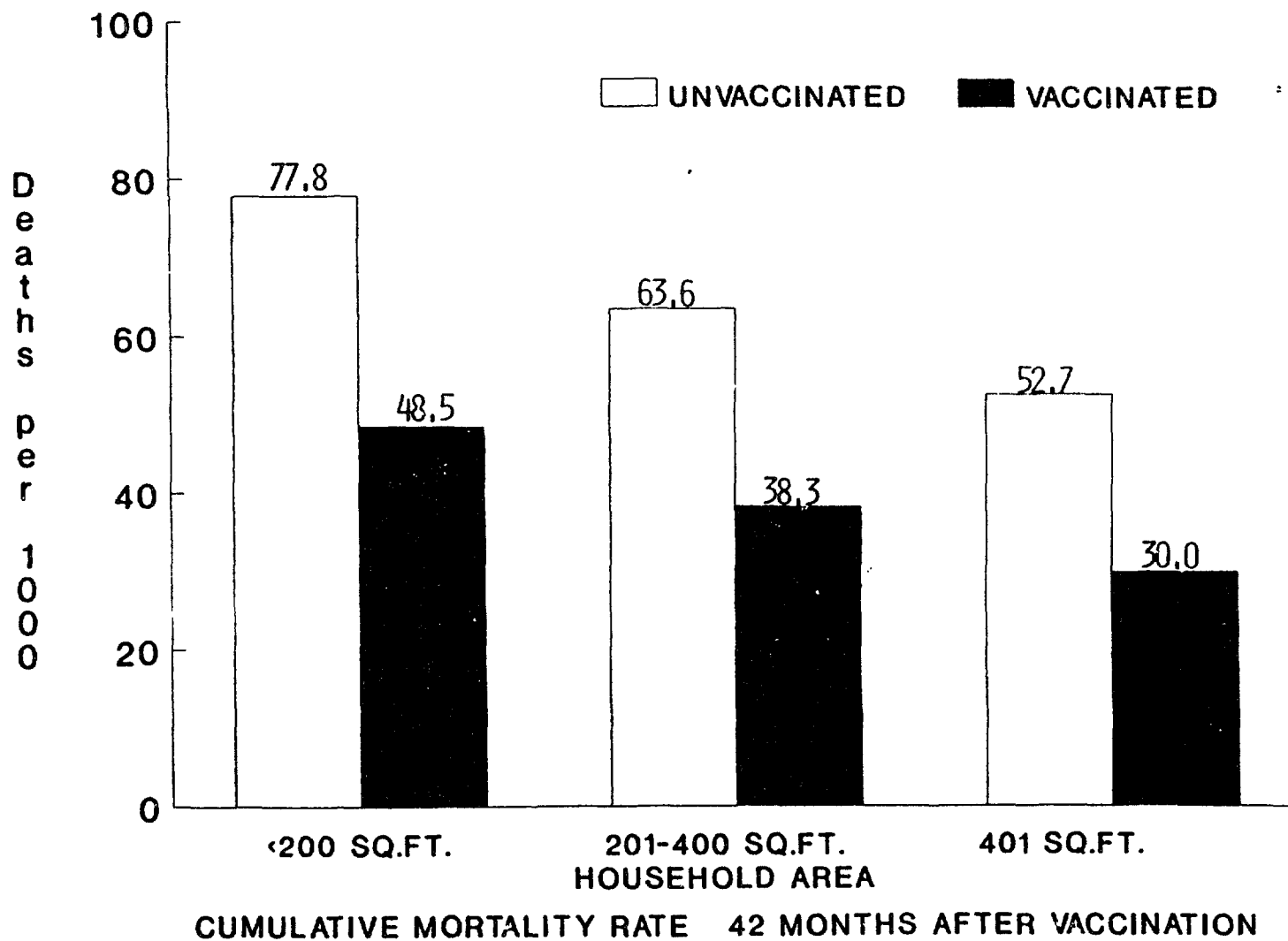
In conclusion, the evidence considered provides no direct or indirect support for the existence of a child replacement effect, which would diminish the contribution of measles vaccination to improved child survival. The available evidence instead indicates that the effect of measles vaccination is sustained over time, and that the greatest benefits from vaccination appear to be found among the most vulnerable children. As such, measles vaccination may reduce not only overall mortality levels but also inequalities between groups in their survival chances.

Potential Selection Bias

A primary issue of concern in all assessments of measles vaccination impact is that vaccinated children represent a special group of children who may have better health and survival prospects, even in the absence of measles vaccination. If this were the case, then the lower mortality risks observed may be due in large part to the special nature of vaccinated children, rather than to measles vaccination *per se*. The studies of measles vaccination impact have adopted a number of different approaches to dealing with the issue of potential selection bias.

The issue of potential selection bias was not directly addressed in the Kasongo study in Zaire. However, the authors presented survival data from the area where measles vaccination had been offered for both the 255 eligible children who were vaccinated as well as the 51 eligible children who were not; many of these latter children may have been self-selected for poorer survival outcomes. Analysis of the survival probabilities of all 306 children together takes into account any possible selection bias between vaccinated and unvaccinated children. The 7-35 month mortality rate for this group was 48.3 per 1000, an increase from the rate of 39.1 per 1000 for vaccinated children alone. However, this still translates into a reduction in mortality relative to the other three control groups of between 30 to 49 percent, indicating a sizeable impact of vaccination upon

FIGURE 5. CUMULATIVE MORTALITY RATES BY MEASLES VACCINATION STATUS AND BY HOUSEHOLD AREA: MATLAB INTERVENTION AREA, 1982-85



mortality even when possible selection bias is taken into account.

In both of the other African studies by Aaby, et al. (1984) and Garenne and Castrille (1986), control groups consisted of unvaccinated children from the same areas where measles vaccination was offered. As such, selection bias may represent an important confounding factor, with controls disproportionately comprised of children who face independently higher mortality risks. This may account in part for the extremely large reductions in mortality reported by the Aaby, et al. in the Guinea-Bissau study.

In the case-control study by Clemens, et al. (1988) in Matlab, little or no effect of measles vaccination upon mortality would have been expected during the first year of the study, since the program was introduced at the end of the annual measles season, unless vaccination acceptors constituted a special group with lower overall mortality risks. The finding that there was no protective effect from measles vaccination during the first year of the study provides strong evidence that measles vaccinees did not constitute a select group with better survival chances from the onset (WHO, 1987). In addition, the reported finding by the authors of a 36 percent mortality risk among vaccinated children was based upon multivariate analysis which controlled for the effects of a number of potentially confounding demographic and socioeconomic characteristics which might differentiate vaccinated from unvaccinated children.

The Matlab cohort study by Koenig, et al. (1990) also considered the issue of potential selection bias from several different perspectives. First, the study examined whether the families of vaccinated and unvaccinated children differed on other indicators of health behavior which might account for lower mortality among the former group of children. No difference between groups was evident with respect to one important indicator of health behavior-- use of contraception. Second, the authors carried out multivariate analysis to control for the effects of a number of potentially confounding variables (birth order, sex, maternal education, and area of household) on which vaccinated and unvaccinated children might differ. The results indicated that even after controlling for these factors, vaccinated children still experienced mortality levels which were 46 percent lower. Lastly, the authors examined whether vaccinated children from the two blocks where measles vaccine was offered may have been self-selected for better survival-- i.e., that a primary reason why children remained unvaccinated in these blocks was that they failed to live long enough to be vaccinated. To take this into account, they constructed a second data set which included all children-- both vaccinated as well as unvaccinated-- from the two blocks where measles vaccination had been offered, and randomly rematched with the pool of unvaccinated children

from the other two blocks. These procedures resulted in 9871 children from each of the two areas. When re-analyzed, the results indicated a slightly reduced but still substantial effect of measles vaccination, with children from the area with measles vaccination still experiencing mortality risks which were 40 percent lower than unvaccinated controls. The authors viewed this figure as a minimum estimate of the effect of measles vaccination upon child mortality in this population.

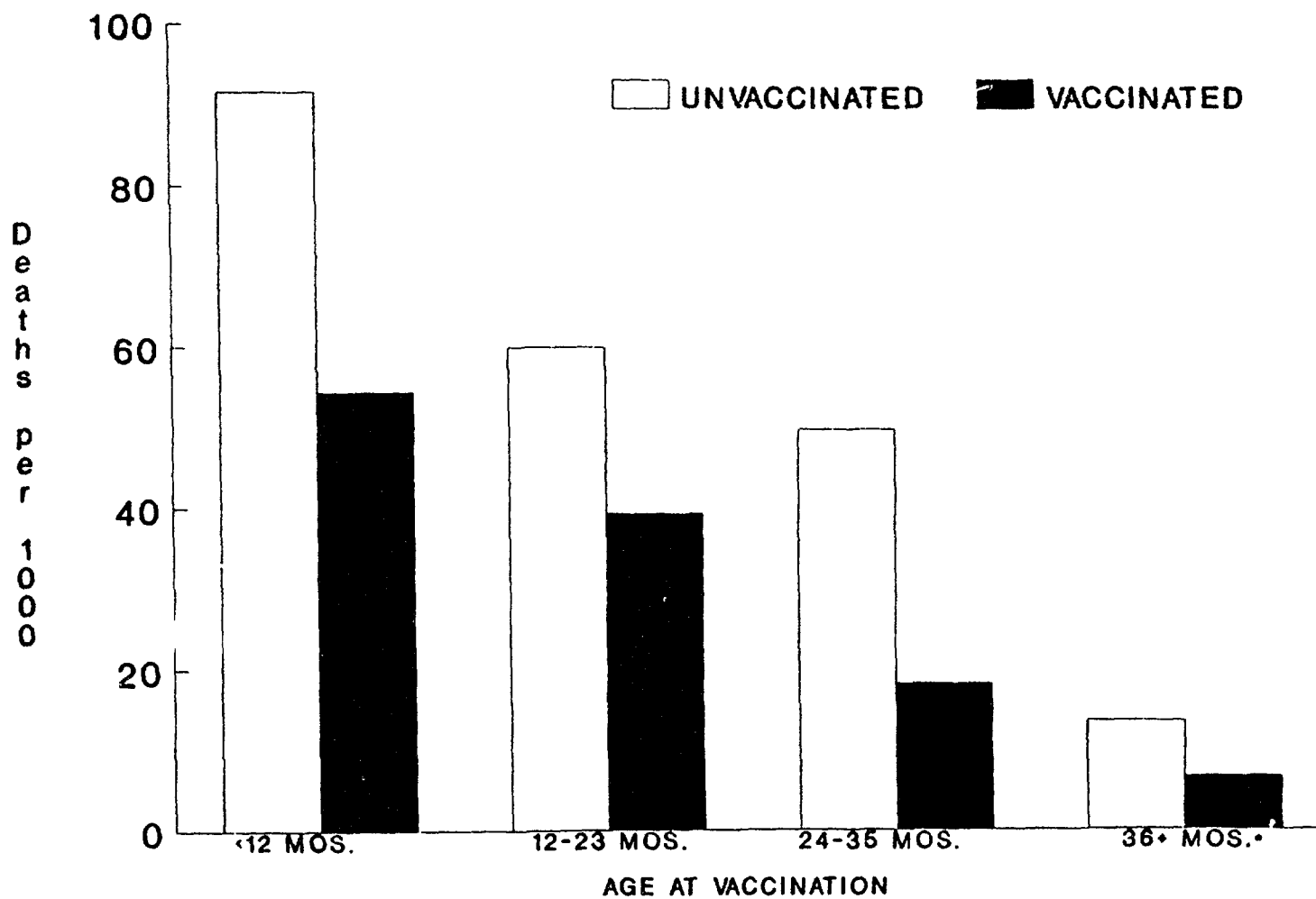
Age at Immunization

A corollary issue of interest concerns the optimal upper and lower age boundaries for measles vaccination. Current WHO guidelines recommend 9 months of age as the optimal age for measles vaccination (WHO, 1982). The focus within immunization programs has generally been on reaching all children from 9 months to 2 years of age. One of the few studies to address this issue has been the study in Bangladesh by Koenig, et al. (1990). The results of life table analysis are summarized in Figure 6. Although the largest absolute reductions in mortality occurred among children who were vaccinated at <12 months of life, substantial and statistically significant reductions were also observed among children vaccinated during the 2nd and 3rd years of life. Although a reduction in mortality was also observed for children vaccinated at above three years, this was not statistically significant, owing to the low mortality rate and small numbers of deaths at these older ages. These findings indicate that extending the priority target group for measles vaccination to all children under 3 years of age is likely to bring about significant further reductions in mortality in settings such as rural Bangladesh.

It has been recognized that in many settings, significant proportions of young children contract measles before nine months of age, frequently with resultant high case-fatality rates. This has spawned efforts toward the development of a new generation of measles vaccines which can be administered at earlier ages, 4-6 months of age (Markowitz, 1990). The incremental gains in mortality reduction from the introduction of these new vaccines will be contingent upon the following conditions:

- 1) The prevalence of measles infections among children <9 months of age
- 2) The level of protective efficacy provided by these new vaccines
- 3) The extent to which existing measles vaccination programs (9+ months) may have already reduced such early measles cases through the elimination of the transmission mechanism through older children/ siblings

FIGURE 6. CUMULATIVE MORTALITY RATE BY MEASLES VACCINATION STATUS AND AGE AT VACCINATION: MATLAB INTERVENTION AREA, 1982-85



CUMULATIVE MORTALITY RATE 36 MONTHS AFTER VACCINATION

*Reflects rates to 24 months after vaccination

SOURCE: KOENIG, ET AL. 1990

TETANUS IMMUNIZATION

Tetanus has been estimated to be responsible for at least 500,000 neonatal deaths annually (Stanfield and Galazka, 1984). Deaths due to neonatal tetanus result largely from the infection of the umbilical stump by Clostridium tetani. Tetanus deaths are extremely rare during the initial days of life, rise rapidly to a peak during the 7th to 8th day of life, then decline through the rest of the neonatal period. Neonatal tetanus is effectively prevented through the maintenance of hygienic conditions at the time of delivery, and/or through passive immunity through the immunization of the mother prior to or during pregnancy.

Tetanus immunization differs from immunization against other childhood diseases such as measles in an important way. Because protection is provided passively through immunization of the mother, the risks of neonatal tetanus and tetanus mortality persist undiminished throughout the mother's reproductive period. This contrasts with immunization against other childhood infectious diseases such as measles, with well-defined risk periods during which the risk of death generally steadily diminishes over time. Thus, in addition to the magnitude of neonatal mortality reductions resulting from maternal tetanus immunization, the issues of duration of immunity and the number of doses required to achieve this immunity become of paramount importance for immunization strategies. In the following sections, empirical evidence bearing on these issues is reviewed.

An extensive literature has accumulated on the effect of tetanus toxoid immunization upon protective antibody levels (see Jones, 1983). However, the number of studies assessing the impact of maternal tetanus immunization upon neonatal mortality levels is much smaller (Table 2).

Reductions in Neonatal Deaths Due to Tetanus

One of the earliest studies from a developing country on the mortality impact of maternal tetanus immunization was a study by Schofield, et al. (1961) in New Guinea carried out during 1959-60. All women in an area where a system of health clinics had been established were offered tetanus toxoid during pregnancy. The size of the study population was relatively small: 234 births and 175 births to mothers who received 2 and 3 injections, respectively, and a control group of 160 births to mothers who received either 0 or 1 injections. Comparison of these three groups showed that two or more tetanus immunizations resulted in a significant reduction in mortality from neonatal tetanus; from 100 per 1000 live births in the control group to 34 per 1000 among births to women receiving two injections. Among births to women receiving three injections, only 1 neonatal

TABLE 2: SUMMARY OF MATERNAL TETANUS IMMUNIZATION STUDIES

STUDY	LOCATION	STUDY PERIOD	STUDY POPULATION	MORTALITY IMPACT	DURATION OF PROTECTION
SCHOFIELD, ET AL.	NEW GUINEAU	1959-1960	0 TT: 86 BIRTHS 1 TT: 74 BIRTHS 2 TT: 234 BIRTHS 3 TT: 175 BIRTHS	REDUCTION IN NEONATAL TETANUS DEATHS FROM 100 PER 1000 TO 34 PER 1000 WITH 2 TT DOSES AND TO 6 PER 1000 WITH 3 TT DOSES	< 12 MONTHS
NEWELL, ET AL.	COLOMBIA	1961-1966	0 TT: 270 AND 347 BIRTHS 1 TT: 224 BIRTHS 2-3 TT: 341 BIRTHS	REDUCTION IN NEONATAL TETANUS DEATHS FROM 78 TO 0 PER 1000 TO WOMEN WITH 2-3 TT DOSES	UP TO 4 YEARS
BLACK, ET AL.	MATLAB, BANGLADESH	1974-1977	0 TT: 4386 BIRTHS 1 TT: 1265 BIRTHS 2 TT: 2990 BIRTHS	33% REDUCTION IN NEONATAL MORTALITY WITH 2 TT DOSES DURING 1975-77 PERIOD	1 TT: UP TO 20 MOS. 2 TT: UP TO 32 MOS.
RAHMAN, ET AL.	MATLAB, BANGLADESH	1974-1979	0 TT: 7237 BIRTHS 1 TT: 486 BIRTHS 2 TT: 956 AND 934 BIRTHS	REDUCTIONS IN NEONATAL MORTALITY OF 18% AND 49% WITH 2 TT DOSES, DEPENDING ON DURATION	1 TT: NS 2 TT: UP TO 5 YEARS
KOENIG, ET AL.	MATLAB, BANGLADESH	1973-1989	0 TT: 10745 BIRTHS 1 TT: 2718 BIRTHS 2 TT 7891 BIRTHS	37% REDUCTION IN NEONATAL MORTALITY WITH 2 TT DOSES DURING 1975-79 PERIOD	1 TT: UP TO 4 YEARS 2 TT: UP TO 15 YRS.

tetanus case out of 175 births was reported, a rate of 6 per 1000 live births.

Further conclusive evidence on the efficacy of tetanus immunization in reducing neonatal tetanus deaths is found in the study by Newell, et al. (1966) in Colombia during the 1961-1966 period. This study consisted of a double-blind experiment in which all registered women were randomly assigned to one of two groups and offered either tetanus toxoid or influenza-virus vaccine. Subsequent births to these women during 1961-66, as well as deaths to these births and specific cause of death, were then followed. The results demonstrated no neonatal tetanus deaths during this period among births to women who had received 2-3 tetanus immunizations, compared to a rate of 78 per 1000 live births among the control group whose mothers received 2-3 injections of the influenza vaccine.

The Matlab study area is the source of much of the conclusive evidence on the effectiveness of maternal tetanus immunization in reducing mortality from neonatal tetanus. As part of a large-scale cholera vaccine trial in the Matlab study area in 1974, non-pregnant adult women and <5 year children received tetanus toxoid as a placebo. A total of 93,000 individuals participated in this trial, which was randomized on an individual basis, with participants receiving either 1 or 2 injections of cholera toxoid or 1 or 2 doses of tetanus toxoid, all on a double-blind basis. Black et al. (1980) analyzed the mortality impact of tetanus toxoid placebo in this trial upon two cohorts of children born during 1975-77 to mothers who participated in the 1974 vaccine trial. A recent study by Koenig, et al. (1991b) extended the original study through the 1975-89 period in the comparison area only, which has remained a population largely unimmunized against tetanus until recently. Finally, Rahman, et al. (1982) analyzed the mortality experience of children born during 1978-79 in the Matlab study area. Two groups of births to mothers immunized against tetanus were evaluated: those who had received tetanus toxoid while not pregnant as part of the 1974 vaccine trial described above, and those who received tetanus toxoid while pregnant in 1978-79, as part of the expanded MCH-family planning program introduced in half of the Matlab study area.

In the absence of conclusive diagnosis of neonatal tetanus deaths, the Bangladesh studies used mortality during days 4-14 of life as a proxy for neonatal tetanus deaths. For the two birth cohorts combined, the study by Black, et al. showed that two injections of tetanus toxoid resulted in a reduction in 4-14 day mortality by 68 percent relative to the control group who received cholera vaccine (from 25 to 8 per 1000), a highly significant effect. The study by Rahman, et al. found that relative to births to unimmunized mothers, two tetanus toxoid injections during pregnancy resulted in statistically significant

reduction in 4-14 day mortality of 69 percent; the effect of having received two tetanus toxoid injections through the vaccine trial an average of 4 1/2 years earlier also resulted in a substantially lower 4-14 day mortality rate (by 41 percent), although this difference was statistically significant in only one of the two areas.

Reductions in Neonatal Mortality

The considerable geographical variability in the importance of neonatal tetanus as a cause of death has long been recognized (Bytchenko, 1966). Data from retrospective surveys in a number of Asian and African countries indicated neonatal tetanus death rates ranging from 3 to 31 per 1000 live births, with tetanus accounting for from 8 to 60 percent of all neonatal deaths (Foster, 1984). In addition to true variability across settings in the importance of neonatal tetanus as a cause of death, these figures are also likely to reflect differences in both under- as well as over-reporting of tetanus as a cause of neonatal death.

The Matlab study area in rural Bangladesh has provided much of the reliable evidence on the actual or potential reductions in mortality resulting from tetanus immunization (Table 3). The study by Black, et al. showed that two injections of tetanus toxoid reduced neonatal mortality in subsequent births by 33 percent. Similar results are obtained from the data presented by Koenig, et al. in the extension of this study. Over the five year period following the vaccine trial (1975-79), two doses of tetanus toxoid were associated with a 37 percent reduction in neonatal mortality. The findings of Rahman, et al. were more variable, with reductions in neonatal mortality ranging as low as 18 percent among births to mothers who received two injections of tetanus toxoid an average of almost five years early as part of the cholera vaccine trial, to as high as 49 percent among births whose mothers had recently been immunized while pregnant with two tetanus toxoid injections, as part of the MCH-family planning intervention program.

Given the very high efficacy of two doses of tetanus toxoid in eliminating tetanus in at least the short-term, accurate data on diagnosed cause of neonatal death among unimmunized populations should also provide a reasonably precise picture of the potential reductions in neonatal mortality resulting from tetanus immunization programs. Table 3 also shows data from other studies in Bangladesh on the prevalence of neonatal tetanus death. Data presented by Koenig, et al. (1991a) on causes of death in the Matlab comparison area, when adjusted for the confounding effects of tetanus immunization delivered through the 1974 cholera vaccine trial described earlier, indicated that tetanus accounted for 27 percent of neonatal deaths in this area

TABLE 3: SUMMARY OF FINDINGS FROM BANGLADESH IMMUNIZATION AND CAUSE OF DEATH STUDIES ON NEONATAL TETANUS

IMMUNIZATION STUDIES	NEONATAL MORTALITY RATE (PER 1000)		% REDUCTION IN NEONATAL MORTALITY
	0 TT	2 TT	
BLACK, ET AL. (1980): 1975-77 BIRTHS	59.7	39.8	33.3%
RAHMAN, ET AL. (1982): IMMUNIZED IN 1974	78.3	63.8	18.5%
IMMUNIZED IN 1978-79	78.3	42.8	48.8%
KOENIG, ET AL. (1991b): 1975-79 BIRTHS	78.2	49.5	36.7%

CAUSE OF DEATH STUDIES	NEONATAL TETANUS MORTALITY RATE (PER 1000)	% OF ALL NEONATAL DEATHS
BHATIA (1989): 1982-83 MATLAB COMPARISON AREA	13.7	20.4%
KOENIG, ET AL. (1991a): 1986-87 MATLAB COMPARISON AREA	18.6*	27.2%*
HLADY, ET AL. (1991): N. BANGLADESH DIVISION	18.2	33.9%

*Adjusted for the effects of the 1974 vaccine trial.

during the 1986-87 period. An earlier study by Bhatia (1989) of 1982-83 infant deaths in the Matlab study area found that tetanus accounted for 20 percent of all neonatal deaths in the comparison area. However, the Bhatia study did not adjust the effects of the 1974 vaccine trial, so that tetanus deaths are likely to have been underestimated in this study.

It should also be emphasized that the earlier findings from Matlab, indicating reductions in neonatal mortality by one-third or more (Black, et al. 1980; Koenig, et al. 1991a) may not be inconsistent with the cause of death estimates of neonatal tetanus cited above. There is evidence of a steady decline in 4-14 day mortality in the Matlab study area since the late 1970s among births to unimmunized mothers (Koenig, et al. 1991b), although the factors which have contributed to this decline remain poorly understood. At the same time, a recent study in a separate area of rural Bangladesh, based upon one year retrospective survey data, reported somewhat higher levels of tetanus-related mortality (34 percent of reported neonatal deaths), raising questions about whether neonatal tetanus levels may be somewhat lower in the Matlab area than for Bangladesh as a whole (Hlady, et al. 1991).

Duration of Immunity

In the Colombian study, no neonatal tetanus deaths were reported among mothers who were immunized during pregnancy with 2 or 3 injections of tetanus toxoid and gave birth over the 1961-66 period (Newell, et al. 1966). This result provided evidence that the protection conferred by maternal tetanus immunization appeared to last for a period of at least four years. Black, et al. (1980) in their Matlab study found that two injections of tetanus toxoid resulted in significantly lower 4-14 day mortality levels through 21-32 months after immunization. The study by Rahman, et al. (1982) in Matlab also provided evidence of extended durations of protection through maternal tetanus immunization. Their findings showed that 1978-79 births to mothers immunized with two injections of tetanus toxoid during the 1974 cholera vaccine trial continued to experience significantly lower 4-14 day mortality rates than among the non-immunized group, indicating that two injections of tetanus toxoid may confer significant levels of protection against tetanus for a duration of as long as five years.

These upper bounds on the duration of immunity reported in all of forementioned studies have been defined by the end of the respective study periods, rather than by a quantifiable diminution in protective immunity. The recent study by Koenig, et al. (1991b), which examined the duration of immunity conferred by tetanus immunization in the 1974 cholera vaccine trial over the

1975-89 period, provides the most conclusive evidence to date on long-term protection conferred by maternal tetanus immunization. Figure 7 shows three-year moving averages in 4-14 day mortality according to 1974 vaccination status for births to mothers residing in the Matlab comparison area. While mortality rates were comparable in the period prior to the vaccine trial (1973-74), a sharp differential in mortality by vaccination status is observed subsequent to the 1974 trial. Although some narrowing in mortality rates between groups is evident over time, the mortality rates for the different groups did not converge over time. Separate analysis by the authors indicated that relative to the unimmunized group, the reduction in 4-14 day mortality among the group receiving two injections of tetanus toxoid was highly statistically significant ($p < .01$) for 8 years and remained significant ($p < .05$) through 1989 (with the exception of 1985-86), a period of 15 years. Thus, even in 1989, the 4-14 day mortality rate for the two injection group was 6 per 1000, compared to 23 per 1000 in the unimmunized group.

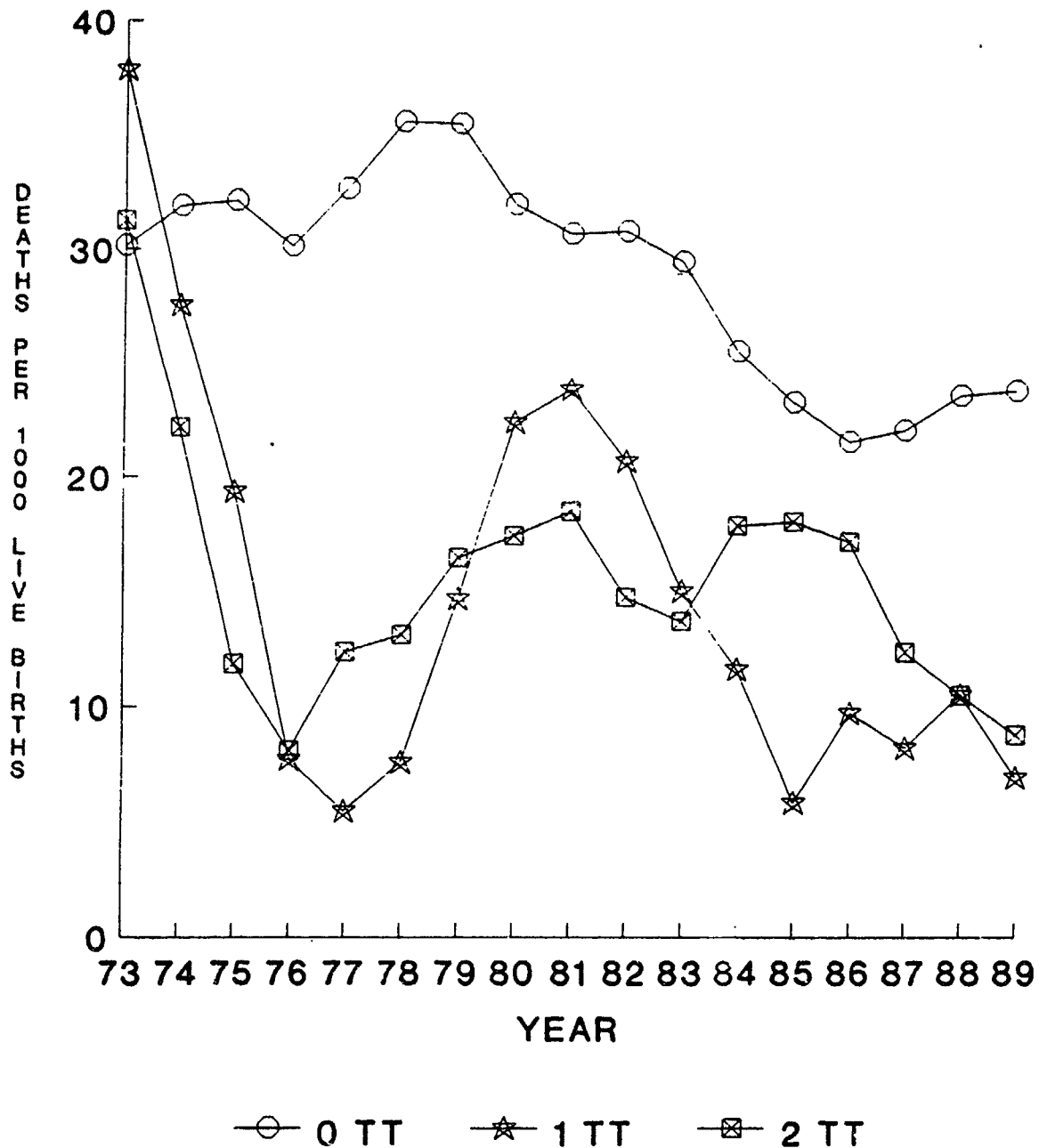
Number of Doses

One Dose

Considerable interest has centered upon the degree of protection provided by one dose of tetanus toxoid, since an effective single dose would greatly simplify the delivery of maternal tetanus immunization. The findings on this issue with respect to mortality impact have been at best inconsistent, and not infrequently contradictory. For example, the New Guinea study found no differences in the neonatal tetanus rates between the small numbers of births to mothers with one injection vs. no injections, with both groups experiencing markedly higher neonatal tetanus rates than those who received 2 or 3 tetanus injections. The Colombian study, on the other hand, reported somewhat lower neonatal tetanus rates among births who received 1 vs. 0 tetanus toxoid injections, although this difference was not statistically significant and the rate for the 1 dose group was still considerably higher than the group who received 2-3 injections (40 vs. 0 per 1000). The small numbers of cases included in both of these studies, however, make definitive conclusions difficult.

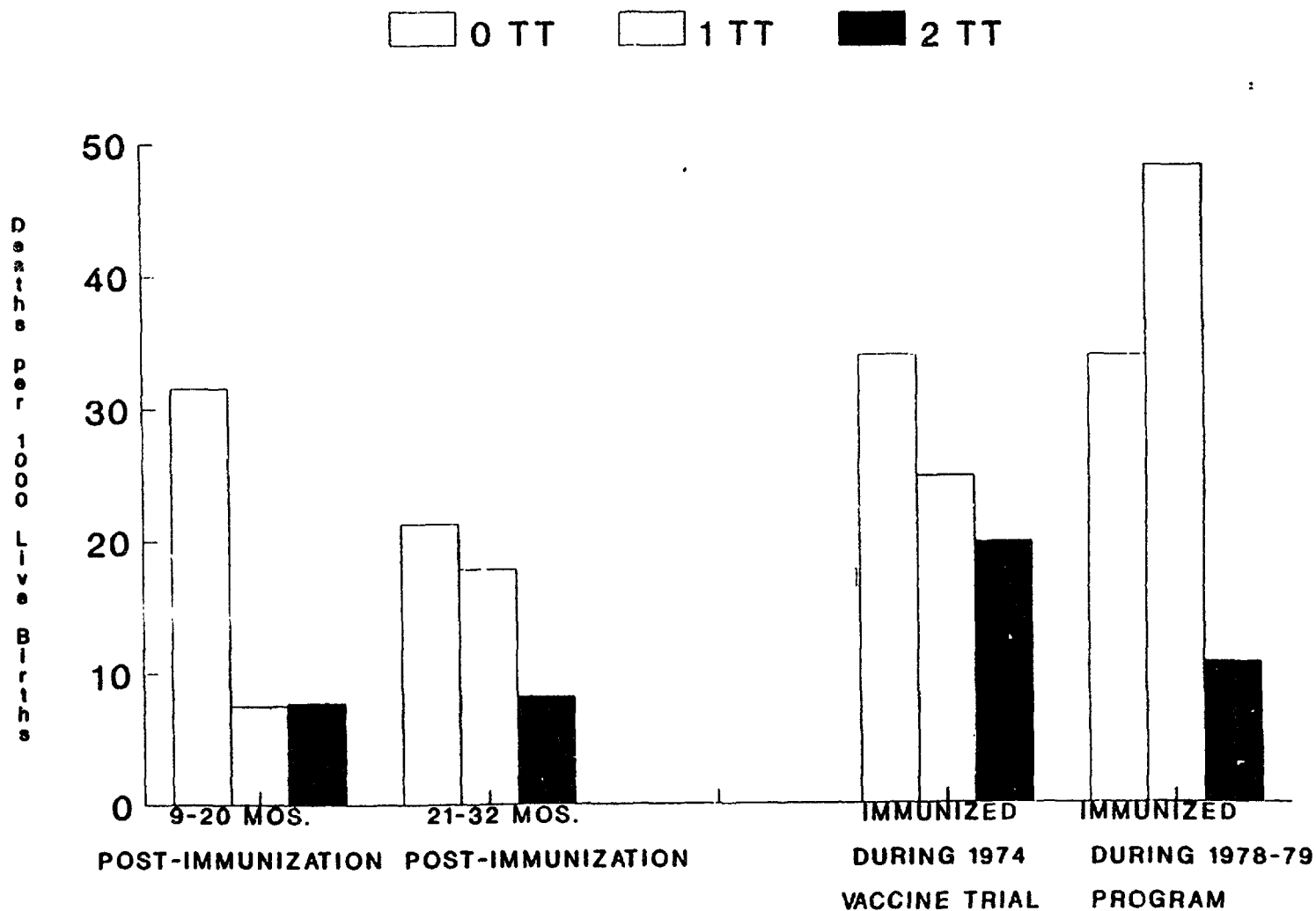
Once again, the most persuasive evidence on the issue of a single tetanus toxoid dose comes from the Matlab study area. However, even within the Matlab study area, the findings on this issue have not been entirely consistent. The effect of one dose is closely linked to the issue of duration of protective immunity. As shown in Figure 8, the study by Black, et al. found that one injection of tetanus toxoid was associated with significantly lower 4-14 day mortality 9-20 months after

FIGURE 7. DURATION OF PROTECTIVE IMMUNITY PROVIDED BY MATERNAL TETANUS TOXOID IMMUNIZATION AGAINST 4-14 DAY MORTALITY: MATLAB COMPARISON AREA, 1973-89



SOURCE: KOENIG, ET AL. (1991b)

FIGURE 8. SUMMARY OF MATLAB FINDINGS ON EFFECTS OF NUMBER OF TETANUS TOXOID DOSES UPON 4-14 DAY MORTALITY



SOURCE: BLACK, ET AL. (1980)

SOURCE: RAIMAN, ET AL. (1982)

immunization, with a mortality rate comparable to the two injection group. However, for the period 21-32 months post-immunization, the rate for this group was no longer significantly lower, but in fact substantially higher than for the two injection group, leading the authors to conclude that a single dose did not provide meaningful protection for longer than 20 months. The findings of the Matlab study by Rahman, et al. led them to conclude one injection of tetanus toxoid did not confer a meaningful level of protection. However, as Figure 8 shows, the results of their study indicated that among the small number of births to women who received only one injection of tetanus toxoid in the 1974 vaccine trial (N= 362), 4-14 day mortality rates were substantially lower than for the unimmunized group and only slightly higher than for the two dose group (34, 25, and 20 per 1000). However, 4-14 day mortality rates among the group who received only a single injection while pregnant through the 1978-79 immunization program were markedly higher than either of the two immunization groups, and twice as high as for the single injection group in the 1974 vaccine trial. This discrepant finding may be explained by the small numbers of births belonging to this group (N=124), as well as the highly selective nature of those who dropped out of the program after receiving only one injection (see subsequent discussion).

The recent study Matlab study by Koenig and colleagues (1991b) provides additional and contrasting evidence on the effect of a single tetanus toxoid dose. As Figure 7 shows, 4-14 day mortality for the one tetanus toxoid injection group closely parallels that for the two injection group not just in the short-run, but for the entire period of observation. The authors' analysis showed that relative to the group of births to unimmunized mothers, lower 4-14 day mortality among the one injection group was statistically significant through 1978-79; for a period of up to four years. At the same time, while not attaining statistical significance, mortality for the one injection group remained below one-half that for the unimmunized group in almost all subsequent years. For the 1975-89 period as a whole, 4-14 day mortality for the one injection group was 12.5 per 1000 live births, significantly lower than for the unimmunized group (28.4 per 1000) and even slightly below that for the two injection group (13.8 per 1000).

3+ Doses

Empirical evidence on the incremental mortality gains from more than two doses of tetanus toxoid is also slender and generally based upon very small study populations. The study in New Guinea found that three injections of tetanus toxoid during pregnancy conferred a higher level of protection against neonatal tetanus compared to two doses, with a reduction in neonatal tetanus mortality from 34.2 deaths per 1000 to 5.7 per 1000

(Schofield, et al. 1961). In contrast, the Colombian study found no difference in neonatal tetanus mortality rates between births whose mothers received 2 versus 3 tetanus injections; both groups experienced no recorded tetanus cases or deaths during the study period of more than four years (Newell, et al. 1966). Finally, data in the Matlab study by Rahman, et al. (1982) allow the comparison of the following 4-14 day mortality rates:

Tetanus Immunization Status	4-14 Day Mortality Rate (per 1000)	(N)
2 doses (1978-79)	10.7	(934)
2 doses (1978-79), 1 dose (1974)	15.6	(64)
2 doses (1978-79), 2 doses (1974)	7.0	(142)

Although the number of cases is small, the results provide no evidence of a consistent further reduction in 4-14 day mortality rates with either 3 or 4 doses of tetanus toxoid, relative to the group who received only two injections while pregnant in 1978-79, during the interval of the study period.

Further corroboration of the Matlab findings through serological studies would be desirable, particularly with respect to the effects of a single dose of tetanus toxoid, given the uncertainties which persist. One limitation common to all of these studies has been the use of 4-14 day mortality as an indicator of tetanus mortality. While most neonatal tetanus deaths are known to be clustered in this period, recent work in Matlab has shown that tetanus may account for only roughly half of all deaths during this age period (Koenig, et al. 1991a), leading to considerable imprecision in this measure as an indicator of tetanus-related mortality. It should also be recognized these studies demonstrate significant reductions in, but not necessarily the elimination of, neonatal deaths due to tetanus-- the stated objective of the Expanded Program on Immunization, and one which might lead to quite different immunization strategies. The recent findings from Matlab nevertheless provide strong evidence that current maternal tetanus immunization strategies may confer significant levels of protection for a much more extended period than has previously been believed. A single injection of tetanus toxoid may also confer a significant degree of protection against tetanus for at least several years, while two injections may provide significant protection throughout much of a woman's reproductive period.

Potential Selection Bias

The issue of potential selection bias among births to vaccinated and unvaccinated mothers has been less of a concern in the studies on the impact of tetanus immunization. One reason is that several of the major studies have been based upon controlled field experiments whose design effectively eliminated the possibility of such selection bias. The field trial by Newell, et al. in Colombia (1966), and the 1974 cholera vaccine trial in Matlab, on which the studies by Black, et al. (1980) and Koenig, et al. (1991b) were based, were both double-blind, controlled field trials. A second reason why selection bias may be of less concern with regard to neonatal immunization studies has been the absence of evidence suggesting that unimmunized mothers differ from immunized mothers in behavior (other than immunization) which predisposes the children of the former to higher risks of neonatal tetanus. A third and related factor has been the absence of evidence suggesting that children at risk of death from tetanus represent an especially vulnerable group who are also at much higher risk of death from other neonatal causes.

Nevertheless, in the studies considered which were not based upon controlled experiments, the possibility of potential selection bias cannot be ruled out. For example, in the study in New Guinea, a primary reason for non-immunization (86 cases) was that mothers came too late in pregnancy to be immunized. The possibility that such women constitute a highly selective group whose children are predisposed toward higher risks of tetanus cannot be ruled out, although the authors view this as unlikely.

Selection bias may have played a more important role in some of the Matlab findings reported by Rahman, et al. (1982). Although maternal tetanus coverage rates subsequently reached very high levels (when offered to all reproductive-aged women), at the time of this study, when made available only during pregnancy, only one-third of eligible women had accepted immunization. It could plausibly be argued that these women may represent a highly selective group who would face lower mortality risks-- and unimmunized women conversely higher mortality risks-- even in the absence of this program. (The dependent variable of 4-14 day mortality leaves open the possibility for selection bias with respect to both tetanus as well non-tetanus deaths, since this measure reflects both). This would help to explain the much larger reduction in neonatal mortality rates among births to mothers who received two injections during the 1978-79 program compared to the other studies from Matlab (49 percent lower). This might also partially account for the absence of a significant effect among the small one dose group, which may consist of a higher proportion of high risk mothers.

Mortality at Later Ages

An additional argument advanced for tetanus immunization is the protection it provides against tetanus beyond the neonatal period. The available empirical evidence on this issue, however, suggests that the magnitude of this additional mortality effect may be quite modest. For example, a study of causes of childhood death in the Matlab comparison area during 1986-87-- where tetanus immunization coverage levels were extremely low-- indicated that tetanus accounted for only 3 percent of post-neonatal and <1 percent of 1-4 year deaths (Koenig, et al. 1991a). Similarly, a population-based study of 1037 deaths to adult women in the Matlab study area during 1976-85 found that only 6 were attributable to tetanus, representing less than 1 percent of all such deaths (Fauveau, et al. 1987). These findings indicate that from the standpoint of mortality impact, the benefits from tetanus immunization will derive largely from a reduction in neonatal tetanus mortality.

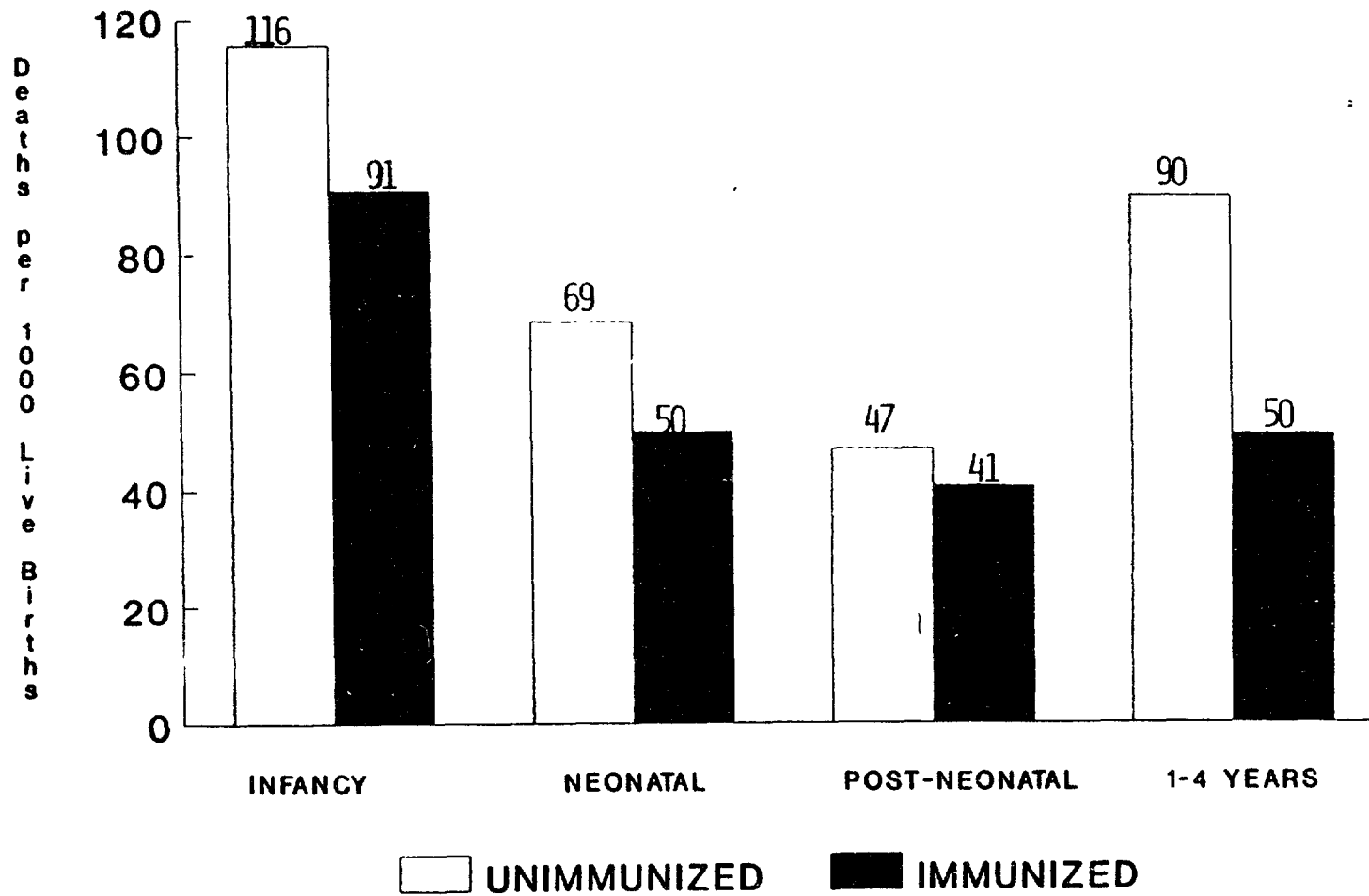
ESTIMATES OF POTENTIAL MORTALITY REDUCTIONS FROM MEASLES AND TETANUS IMMUNIZATION

The recent study by Koenig, et al. (1991a) allows the estimation of the mortality impact of measles and tetanus immunization for rural Bangladeshi children. In this study, the survival status of a cohort of 8161 births, representing all births within the Matlab comparison area during 1982-83, was followed through the end of 1987 to estimate <5 year mortality levels in a largely unimmunized population. The authors then applied the previously reported findings from Matlab on cause of death and vaccination impact, in addition to data on the age distribution of mortality, applying the most liberal estimate of mortality reduction for each case, to estimate reductions in mortality based upon the elimination of deaths from these causes. The results of this exercise for measles and tetanus mortality are shown in Figure 9.

For this population of children, the elimination of tetanus and measles through immunization could be expected to reduce infant mortality levels from the previous level of 116 per 1000 live births to 91 per 1000 live births. It is apparent that most of this reduction would occur through a reduction in neonatal mortality levels (from 69 to 50 per 1000 live births) as a result of tetanus immunization; the reduction in post-neonatal mortality levels will be quite modest (from 47 to 41 per 1000 live births). A marked decline in 1-4 year mortality is also evident as a result of large effect of measles vaccination, with mortality between these ages declining from 90 per 1000 to 50 per 1000 live

births. Overall, the impact of eliminating measles and tetanus mortality through immunization would be to reduce <5 year mortality from the baseline level of 206 per 1000 to 140 per 1000 live births, a reduction of 32 percent. Two caveats are in order. First, as the authors point out, a number of assumptions have been built into these estimates, with the result that the actual reductions in mortality could be either over- or underestimated by these figures. Second, these estimates are specific to one area in rural Bangladesh, and the likelihood exists that likely mortality reductions might vary considerably in other settings, or even in other parts of Bangladesh.

FIGURE 9. ESTIMATED REDUCTIONS IN INFANT AND CHILD MORTALITY FROM TETANUS AND MEASLES IMMUNIZATION: 1982-83 MATLAB COMPARISON AREA BIRTH COHORT



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