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Impact of packaged interventions on neonatal health: a review of the evidence

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A disproportionate burden of infant and under-five childhood mortality occurs during the neonatal period, usually within a few days of birth and against a backdrop of socio-economic deprivation in developing countries. To guide programmes aimed at averting these 4 million annual deaths, recent reviews have evaluated the efficacy and cost-effectiveness of individual interventions during the antenatal, intrapartum and postnatal periods in reducing neonatal mortality, and packages of interventions have been proposed for wide-scale implementation. However, no systematic review of the empirical data on packages of interventions, including consideration of community-based intervention packages, has yet been performed. To address this gap, we reviewed peer-reviewed journals and grey literature to evaluate the content, impact, efficacy (implementation under ideal circumstances), effectiveness (implementation within health systems), type of provider, and cost of packages of interventions reporting neonatal health outcomes. Studies employing more than one biologically plausible neonatal health intervention (i.e. package) and reporting neonatal morbidity or mortality outcomes were included. Studies were ordered by study design and mortality stratum, and their component interventions classified by time period of delivery and service delivery mode.

We found 41 studies that implemented packages of interventions and reported neonatal health outcomes, including 19 randomized controlled trials. True effectiveness trials conducted at scale in health systems were completely lacking. No study targeted women prior to conception, antenatal interventions were largely micronutrient supplementation studies, and intrapartum interventions were limited principally to clean delivery. Few studies approximated complete packages recommended in *The Lancet's* Neonatal Survival Series. Interventions appeared largely bundled out of convenience or funding requirements, rather than based on anticipated synergistic effects, like service delivery mode or cost-effectiveness. Only two studies reported cost-effectiveness data. The evidence base for the impact of neonatal health intervention packages is a weak foundation for guiding effective implementation of public health programmes addressing neonatal health. Significant investment in effectiveness trials carefully tailored to local health needs and conducted at scale in developing countries is required.

Keywords Care-seeking, evidence, health systems, interventions, neonatal mortality, newborn, community mobilization, service delivery, cost-effectiveness, effectiveness

Introduction

Child survival initiatives have made significant strides in reducing under-five child mortality in recent decades. As the burden of post-neonatal deaths declines, neonatal deaths—deaths within the first 28 days of life—comprise an increasing share, currently estimated at 38% of all under-five deaths and

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KEY MESSAGES

- There is a dearth of data available on the process of and impact from the implementation of packages of interventions to improve neonatal health and survival.
- Patterns of packaging of neonatal care interventions in published studies rarely conform to recommendations set forth in *The Lancet's* 2005 Neonatal Survival Series, using common service delivery modes, time period of intervention and synergistic combinations of interventions.
- A key challenge for effective implementation of neonatal intervention packages is developing and sustaining constructive linkages between families, communities and health facilities via community mobilization and education, outreach services, referral capacity and engaging existing cadres of community health workers in neonatal health.
- Cost and impact data for implementation of scalable packages of evidence-based interventions in real-life health systems is crucial for the development of effective national strategies to save newborn lives.

totalling 4 million annually (Darmstadt *et al*. 2005; Lawn *et al*. 2005). Ninety-nine per cent of neonatal deaths occur in developing countries (Lawn *et al*. 2005), usually soon after birth, at home (Black *et al*. 2003) against a backdrop of poverty, suboptimal care-seeking and weak health systems (Lawn *et al*. 2004; Bhutta *et al*. 2005; Lawn *et al*. 2005).

Fostering social development, reducing inequity and promoting economic growth among the poor in developing countries are important objectives addressed by the Millennium Development Goals (Sachs and McArthur 2005). There is an immediate need, however, for wide-scale implementation of evidence-based, cost-effective health programmes and interventions to improve newborn health outcomes. Meeting Millennium Development Goal (MDG) 4, which calls for a two-thirds reduction in under-five mortality by 2015, will require a significant reduction in neonatal deaths, particularly early neonatal deaths. A recent analysis of the evidence base for efficacy (i.e. impact under ideal conditions) and effectiveness (i.e. impact within a health system) of interventions, and their cost-effectiveness, suggested that feasible, cost-effective interventions exist that could prevent roughly two-thirds of all neonatal deaths (Darmstadt *et al*. 2005). Many of these interventions are relatively simple and highly cost-effective (Adam *et al*. 2005).

While evidence suggests that most neonatal deaths can be prevented even in settings with high neonatal mortality and weak health systems (Darmstadt *et al*. 2005), programmes face serious logistical challenges in delivering interventions at scale, particularly where access to health services is poor (Knippenberg *et al*. 2005). Health systems in much of the world are hobbled by bureaucracy, corruption and lack of financial and human resources (Freedman *et al*. 2005). Cost-effective interventions rarely reach people who need them most, as programmes delivering these interventions often suffer from intermittent coverage, poor quality, inequitable access and lack of long-term objectives (Victora *et al*. 2004b).

A recent series in *The Lancet* addressed deficiencies in health systems, from inequities to logistical and resource constraints, and drew attention to the dearth of health systems effectiveness studies (Haines and Victora 2004). The weak evidence base yields little consensus about how best to strengthen health systems. Travis *et al*. (2004) note an urgent need to translate the limited existing knowledge about intervention effectiveness into practice. However, strengthening health systems is costly and requires long-term investment. A recent global meeting convened by the World Health Organization (WHO) identified this lack of health systems research as a critical barrier to achieving the MDGs (Task Force on Health Systems Research 2004), and advocated for increased resources to generate the data needed to design equitable, effective, efficient and sustainable health systems. Health systems research must also consider how the quality and accessibility of health systems (Box 1) vary widely by region and even within countries, as do factors that promote programme sustainability and scalability (Bhutta 2005).

The growing body of evidence from clinical and programme research suggests that effective neonatal health interventions could be bundled together to enhance cost-effectiveness and to suit existing health systems (Victora *et al*. 2004b; Darmstadt *et al*. 2005). The 2003 series in *The Lancet* by the Bellagio Child Survival Study Group hypothesized that under conditions of optimal delivery—universal coverage and acceptance—evidence-based child and neonatal health interventions could prevent 63% of under-five child deaths and up to 55% of neonatal deaths (Jones *et al*. 2003). While this study highlighted the growing fraction of neonatal deaths, its analysis covered the efficacy of a relatively limited range of single interventions that impact neonatal health.

Subsequently, *The Lancet's* Neonatal Survival Series built upon the concept of organizing and packaging neonatal health interventions for effective delivery by three service delivery modes: family-community, outreach, or facility-based clinical care (World Bank 2004; Bhutta *et al*. 2005; Darmstadt *et al*. 2005). Presenting analyses from a health systems perspective, *The Lancet's* series recommended that interventions be packaged according to target population, time period of implementation and service delivery mode (Bhutta *et al*. 2005; Knippenberg *et al*. 2005). As a newborn infant's health is intrinsically linked with its mother's, incorporating newborn care into existing Safe Motherhood as well as Child Survival programmes has also been suggested as a cost-effective way to bundle interventions to simultaneously improve neonatal, maternal and child health outcomes (Bhutta *et al*. 2005; Knippenberg *et al*. 2005). However, thus far there has been no published systematic

Box 1 Variations in health systems

Well-functioning health system

- Health clinics and referral facilities are accessible to rural and urban populations, including the poorest minority/disenfranchised groups.
- Facilities are sufficiently stocked with appropriate supplies.
- Health staff are paid on schedule and provided sufficient training and supervision.
- Schools and communities incorporate health education.
- Skilled attendants and referral facilities are available where facility-based births are not possible.

Weak to transitional health system

- Government health clinics or facilities exist, but are spread over large distances and are inaccessible to significant portions of the population.
- Trained health staff are scarce among rural populations, especially poor and minority/disenfranchised groups.
- Stock-outs of medicine and basic supplies are common.
- Severe budget constraints and/or corruption exist in health systems.
- Traditional birth attendants have limited training from skilled attendants.

Nonexistent to poorly functioning health system

- Government health facilities are nonexistent or inaccessible to the vast majority of the population.
- Local private practitioners provide the majority of services.
- Skilled health care workers are scarce or nonexistent.
- Facility-based births are rare; untrained traditional birth attendants or relatives attend most births.

review of the empirical evidence for the impact of packages of interventions on neonatal health outcomes, nor has there been an assessment of the efficacy or effectiveness of such packages.

This review evaluates available data on the implementation of packages of interventions (i.e. two or more biologically plausible neonatal health interventions) intended to reduce neonatal mortality and morbidity, and identifies research gaps in the implementation of packages of neonatal health interventions in health systems. The scope of this review is limited to interventions addressing proximal (direct) determinants of neonatal outcomes rather than distal determinants such as economic development and social or gender inequities, because of the lack of empirical data quantifying how distal determinants impact neonatal outcomes.

Methods

Selection of interventions

We evaluated the available evidence in the global literature for the impact of a wide range of interventions during the antenatal, intrapartum and postnatal periods on perinatal and neonatal health status outcomes. We used results of previously published systematic reviews of the evidence for single interventions that had estimated mortality impacts using peer-reviewed studies and expert opinion (Bhutta *et al*. 2005; Darmstadt *et al*. 2005). Selection of individual interventions as package components was based on biological plausibility and potential feasibility of inclusion in maternal, neonatal and/or child health care programmes. Those chosen for review are shown in Box 2.

Only studies from developing countries testing packages of these health interventions (i.e. more than one component intervention) were considered eligible for inclusion. We considered iron/folic acid supplementation during the antenatal period a single intervention for the purposes of this review, as the supplements were usually administered together (only two studies administered iron without folic acid) (Bouvier *et al*. 1997; Ramakrishnan *et al*. 2003). Although efforts were made to identify health systems studies measuring the effectiveness of intervention packages, no such studies were found. Two of the studies we reviewed approximated effectiveness trials of a package of interventions; one (Srinivasan *et al*. 1995) offered a package of interventions but study arms differed only in the degree of provider training, and the other (Yan 1989) lacked a control or comparison group and provided little detail about implementation, making both fall short of the criteria for a true effectiveness trial of a package of interventions.

Literature search and review strategy

The search for evidence explored all available electronic health and social science reference libraries, including PubMed/MEDLINE, POPLINE, LILACS, PAHO, African Index Medicus and EMRO. Manual reviews were conducted of Safe Motherhood and Child Survival monographs, including programme evaluations and technical reports. Evidence from the Cochrane Library and the WHO Reproductive Health Library was reviewed where applicable. Further information and unpublished material was solicited directly from agencies, institutions and leading public health researchers working in developing countries. Papers in languages other than English, provided an abstract was available in English, were reviewed. While we prioritized the identification of randomized controlled trials (RCTs), the scarcity of developing country RCTs comparing packages of interventions and the theoretical limitations of RCTs, including lack of generalizability and inappropriateness

Box 2 Neonatal health interventions reviewed

Antenatal interventions	Intrapartum interventions	Postnatal interventions
• Iodine supplementation[a]	• Clean delivery practices[a]	• Breastfeeding[a]
• Maternal deworming[a]	• Vaginal and newborn skin antisepsis[b]	• Prevention and management of neonatal hypoglycaemia[a]
• Syphilis screening and treatment[a]	• Antepartum haemorrhage treatment	• Care in peripheral health facilities[b]
• Tetanus toxoid immunization[a]	• Assisted vaginal delivery	• Hepatitis B vaccination[b]
• Antibiotics for preterm premature rupture of the membranes[b]	• Corticosteroids for preterm labour	• Kangaroo mother care[b]
• Antibiotics for UTI/STD/asymptomatic bacteriuria[b]	• Diagnosis and management of breech, multiple births	• Maternal health education[b]
• Balanced protein-energy supplementation[b]	• Emergency obstetric care	• Newborn resuscitation[b]
• Malaria chemoprophylaxis, including IPT[b]	• Emergency transport for obstetric complications	• Pneumonia case management[b]
• Malaria prevention using impregnated bednets[b]	• Labour surveillance and use of partograph	• Prevention and management of neonatal hypothermia[b]
• Periconceptual folic acid supplementation[b]	• Prevention of maternal-to-child transmission of HIV	• Prevention of ophthalmia neonatorum[b]
• Antenatal folic acid supplementation	• Prevention of preterm labour: magnesium, calcium, fish oil	• Topical emollient therapy[b]
• Antibiotics for bacterial vaginosis	• Skilled birth attendants	• TBA/CHW training[b]
• Antibiotics for preterm labour	• Treatment of pregnancy-induced hypertension	• ARV treatment for HIV
• Birth preparedness and emergency planning		• Birth spacing
• Corticosteroids for preterm labour		• Care of LBW infants
• Iron supplementation		• Delayed umbilical cord clamping
• Maternal pneumococcal immunization		• Emergency transport (newborn)
• Multiple micronutrient supplementation		• Hyperbilirubinaemia screening
• Pre-eclampsia and eclampsia prevention and treatment		• Injectable use of antibiotics by CHWs
• Promotion of smoking cessation in pregnancy		• Neonatal vitamin A supplementation
• Vitamin A supplementation		• Postnatal visitation
• Zinc supplementation		• Vitamin K prophylaxis

[a]Clear evidence of efficacy, highly recommended for inclusion in programmes.

[b]Some evidence of efficacy, recommended for inclusion in programmes but requires further research (see Bhutta *et al*. 2005).

ARV = antiretroviral; CHW = community health worker; HIV = human immunodeficiency virus; IPT = intermittent presumptive treatment; LBW = low birth weight; STD = sexually transmitted disease; TBA = traditional birth attendant; UTI = urinary tract infection.

in health systems settings (Horwitz 1987; Rabeneck *et al*. 1992; Concato and Horwitz 2004; Victora *et al*. 2004a), led us to include other study designs as well, namely prospective cohort, quasi-experimental and retrospective designs.

Priority was given to evidence of impact on perinatal or neonatal mortality, but when data on these primary health status outcomes was nonexistent, we assessed the evidence for impact on determinants of mortality and morbidity, including outcomes such as reductions in prematurity, birth asphyxia incidence, low birth weight (LBW) rates, breastfeeding and infectious disease morbidity (i.e. 'secondary outcomes'). Studies of interventions such as population-based nutrition education or hand-washing interventions that included but did not quantify impact for neonates (Luby *et al*. 2004; Sobel *et al*. 2004; Jones *et al*. 2005; Luby *et al*. 2005) were considered beyond the scope of this paper.

Qualitative description and ranking of studies

Several different systems of standard ranking criteria have been devised and applied to international clinical trial data, such as those designed by the National Institute for Clinical Excellence (NICE), the Scottish Intercollegiate Guidelines Network and the Cochrane Collaboration (SIGN 2001; Jackson and Waters 2004; NICE 2004). Their application to non-randomized studies remains of limited use, however, as the criteria assume a high degree of design and analytical robustness rarely found in developing country field trials. We attempted to use these scoring schemas in our review, but the criteria failed to apply in all but a handful of cases due to the small number of studies identified for review and the variability in design and analytical rigour among them.

In lieu of adopting an international standard scoring schema, studies were evaluated for size, design quality and setting (including service delivery mode and WHO neonatal mortality stratum) (Zupan and Aahman 2005). Two principal reviewers independently evaluated all studies, and a common reporting matrix was employed in summarizing findings (Tables 1–4). Studies were classified into three descending tiers of study design quality: (1) RCTs (Tables 1, 2); (2) prospective cohort trials with control/comparison groups (Table 3); and (3) retrospective or quasi-experimental non-controlled trials (Table 4). We found no data on whether appropriate statistical adjustment was made for older cluster-randomized studies (e.g. Kielmann *et al*. 1978a,b), which may weaken the accuracy of these mortality estimates in comparison with newer cluster-randomized RCTs that clearly specified statistical adjustment.

Component interventions in each package were identified and categorized according to time period of delivery (e.g. periconceptual, antenatal, intrapartum or postnatal). The service delivery mode by which each component intervention was implemented was classified as family-community, outreach, or facility-based clinical care. Family-community interventions were defined as those engaging family members or volunteer

community members as providers, including adoption of improved care practices and appropriate care-seeking for illness (e.g. behaviour change communications and accompanying community mobilization strategies, education to improve care-seeking, and community-based case management of illnesses by community health workers). Outreach interventions were defined as interventions delivered periodically by trained providers. Facility-based clinical care was delivered within the formal health care system by providers skilled in managing acute clinical problems. In any cases of inter-observer disagreement, which occurred rarely, most commonly in interventions including training of traditional birth attendants (TBAs) via outreach to encourage family-community care, the two reviewers examined the original paper together to mutually agree on a classification. Studies were sorted by design and ordered hierarchically in a matrix to maximize clustering of interventions with like service delivery modes. The empirical body of evidence for the impact of packaged interventions was then compared with recent recommendations and impact modelling in *The Lancet's* Neonatal Survival Series recommendations and impact modelling (Bhutta *et al*. 2005; Darmstadt *et al*. 2005).

Results

We found a paucity of data from developing countries and poor rates of inclusion of a number of key evidence-based interventions. Forty-one studies from developing countries that included a package of interventions for neonates were identified for in-depth review, including 19 RCTs, 16 prospective cohort studies, and six retrospective/quasi-experimental studies. Sample size ranged from 126 women (Qureshi *et al*. 1973; Bouvier *et al*. 1997) to more than 100 000 births (Meegan *et al*. 2001); however, most packages were implemented with relatively small sample sizes, and quality and publication source varied widely.

Study design

RCTs were subdivided into two types: (1) those involving interventions delivered across varying time periods and service delivery modes ($n = 7$) (Table 1), and (2) those involving only antenatal interventions ($n = 12$), most of which were limited exclusively to outreach-based micronutrient supplementation ($n = 10$) (Table 2). By comparison, prospective studies were heavily oriented towards postnatal interventions (Table 3). All 16 prospective studies had some postnatal component, and seven of these incorporated *only* postnatal interventions. No clear patterns emerged from the retrospective/quasi-experimental studies, due in part to their small number ($n = 6$) (Table 4).

Service delivery mode

Studies tended to cluster interventions by service delivery mode; 27 of the 41 studies employed a single service delivery mode (commonly outreach). In cases where more than one service delivery mode was used, most commonly there was a mix of all three modes, but this was observed almost exclusively during the postnatal period.

Across all time periods, interventions in packages were delivered predominantly via the family-community service delivery mode (95/195), especially clean home delivery (Table 5). Clinical (43/195) and outreach (57/195) service delivery modes were also used less commonly, although outreach was the most common among antenatal interventions (Table 5). This was heavily influenced, however, by the 12 antenatal micronutrient supplementation RCTs (Table 2), which accounted for 27 of 39 antenatal outreach interventions. During the antenatal and intrapartum periods, clinical interventions—interventions normally provided at a clinic or hospital facility by a skilled health care provider—were included in only three studies (Yan 1989; Srinivasan *et al*. 1995; Smith *et al*. 2000). Many evidence-based outreach (e.g. periconceptual folic acid supplementation, syphilis screening and treatment, intermittent presumptive treatment for malaria, detection and treatment of asymptomatic bacteriuria) and clinical interventions [e.g. antibiotics for preterm premature rupture of membranes (PPROM), corticosteroids for preterm labour] were not included in any packages. Screening for pregnancy-induced hypertension was conducted in only one study (Table 1) (Srinivasan *et al*. 1995).

Studies primarily using the family-community service delivery mode were more likely than others to provide a continuum of care from pregnancy to childbirth and the postnatal period. An illustrative example is Dutt and Srinivasa's engagement of Anganwadi workers [a type of community health worker (CHW) under the Indian government's Integrated Child Development Services scheme] as community-based providers of antenatal supplement and tetanus toxoid immunization, facilitators of referral and emergency transport for maternal and newborn complications, and educators during postnatal home visits about family planning and newborn care (Dutt and Srinivasa 1997). This approach achieved 100% coverage of antenatal care and TT immunization for all mothers and eliminated neonatal deaths due to tetanus and measles, resulting in a 15% decline in the neonatal mortality rate.

Service delivery mode was not closely linked to study design. Except for antenatal-only RCTs, which *only* used outreach for delivery, there were examples in all three study design categories of studies (12/41) that mixed family-community, outreach and clinic-based service delivery modes, yet included a limited number of evidence-based interventions.

Time period of interventions

No interventions in any package targeted women of reproductive age periconceptually, the critical period for folic acid supplementation (Bhutta *et al*. 2005; Darmstadt *et al*. 2005). Rather, folic acid supplementation was frequently included in antenatal packages ($n = 10$), in spite of a lack of evidence that it improves neonatal health outcomes. Antenatal interventions were almost exclusively restricted to micronutrient supplementation trials ($n = 12$), tetanus toxoid immunization ($n = 7$) and/or birth preparedness ($n = 5$). Birth preparedness and tetanus toxoid immunization were implemented together in only two studies, using multiple service delivery modes (Tables 1, 2) (Greenwood *et al*. 1990; Srinivasan *et al*. 1995).

Intrapartum interventions overwhelmingly involved promotion of clean delivery. Of the 16 studies that incorporated any intrapartum intervention, 14 included clean delivery practices. Among RCTs, most studies limited intrapartum interventions to clean delivery, except for one study that utilized skilled attendants at delivery (Srinivasan *et al*. 1995). Similarly, among studies of other designs that included intrapartum

Table 1 Intervention components of packages tested in randomized controlled trials

				Antenatal					IP		Postnatal														
RCTs with postpartum interventions	**No. of subjects**	**Country, setting, location**	**Objective**	Planning for birth and emergencies	Tetanus toxoid immunization	Pre-eclampsia/eclampsia prevention & treatment	Iron & folic acid supplementation	Protein-energy supplementation	Clean delivery practices	Skilled attendant	TBA/CHW training	Postpartum visitation	Maternal health education	Pneumonia case management	Newborn resuscitation	Prevent & manage neonatal hypothermia	Care of LBW Infants	Hyperbilirubinaemia screening	Kangaroo mother care	Prevent & manage hypoglycaemia	Community mobilization	Health systems integration	**Mortality stratum**	**Primary outcomes**	**Secondary outcomes**
Arif & Arif 1999	$n = 361$ LBW (151 case; 211 control)	Pakistan, urban, hospital	Randomize LBW babies to incubator care by mother's bedside (nursed by mothers) or care in nursery by nurses.										C	C		C	C	C	C	C		X	4	57% decline in IMR ($P < 0.001$)	
Jokhio *et al.* 2005	$n = 19\,557$ pregnant women (10 114 intervention)	Pakistan, rural, community	Cluster-randomize pregnant women to two groups: usual care or improved services (trained TBAs, delivery kits, enhanced referral, antenatal care, and postpartum visits).	O		FC			O		O	FC	FC										4	30% decline in PMR (CI: 18–41%) 29% decline in NMR (CI: 17–38%) 31% decline in stillbirths (CI: 17–43%)	
Kielmann *et al.* 1978a & b	$n = 2360$ children <3 (960 NUT/MC; 400 MC; 600 NUT)	India, rural, community	Randomize children, including newborns, to nutrition care (NUT), nutrition care plus medical care (NUT + MC) or medical care (MC).		FC		FC	FC			FC	FC	FC	FC							X	3	41% decline in PMR	Prenatal care visits negatively correlated with PMR; 50% reduction in pneumonia mortality.

Kumar *et al.* 2004	$n = 3274$ pregnant women	India (Uttar Pradesh), rural, community	Evaluate the impact of an essential newborn care package on neonatal mortality in the context of community mobilization efforts.	FC					FC		FC	FC	FC			FC	FC		FC		X		4	50% decline in NMR within intervention group	Improved delivery practices, breastfeeding initiation, and KMC adoption.
Manandhar *et al.* 2004	$n = 28\,391$ pregnant women (2271 intervention)	Nepal, rural, community	Cluster-randomize villages, then organize village women's groups in intervention areas to hold monthly meetings to encourage participatory design and implementation of local programmes to address obstetric and perinatal problems. Health systems strengthening funded when women's groups requested it.	FC					FC		FC	FC			C	C		C			X		3	30% decline in NMR (CI: 6–47%)	No morbidity change. Positive behaviour change (ANC, feeding, care seeking, clean delivery kit use).
Rahman 1982	$n = 1760$ pregnant women	Bangladesh, rural, community	Analyse impact of TBA training (maternal nutrition and newborn care practices) and tetanus toxoid immunization		O				FC		FC	O		C	FC		C						3	TBA: 72% NMR decline (CI: 57–84%) TT: 54% NMR decline (CI: 35–71%)	
Srinivasan *et al.* 1995	$n = 871$ pregnant women, ($n = 294$ high-risk package, $n = 242$ standard package, $n = 335$ controls)	India, rural, community & hospital	Women were randomized to receive 1 of 3 packages: 1) High-Risk Package (HR) in which trained midwives identified high-risk pregnancies and intervened accordingly, 2) Tamil Nadu (TNG) package included trained midwives but not high-risk pregnancy identification, and 3) control group that received a basic package of government-approved care.	O	O		FC		O	C	O	FC		O								X	3	No impact of training on mortality of infants/mothers most likely to be referred.	No difference in birth weight.
Total interventions (by intervention type)				**4**	**3**	**1**	**2**	**1**	**4**	**1**	**6**	**6**	**3**	**3**	**2**	**2**	**2**	**1**	**1**	**1**					

Notes: Key to service delivery mode: Family/community (FC); Outreach (O); Clinical (C).

ANC = antenatal care; CI = confidence interval; IMR = infant mortality rate; IP = intrapartum; KMC = Kangaroo mother care; LBW = low birth weight; NMR = neonatal mortality rate; PMR = perinatal mortality rate; RCT = randomized controlled trial; TBA = traditional birth attendant; TT = tetanus toxoid.

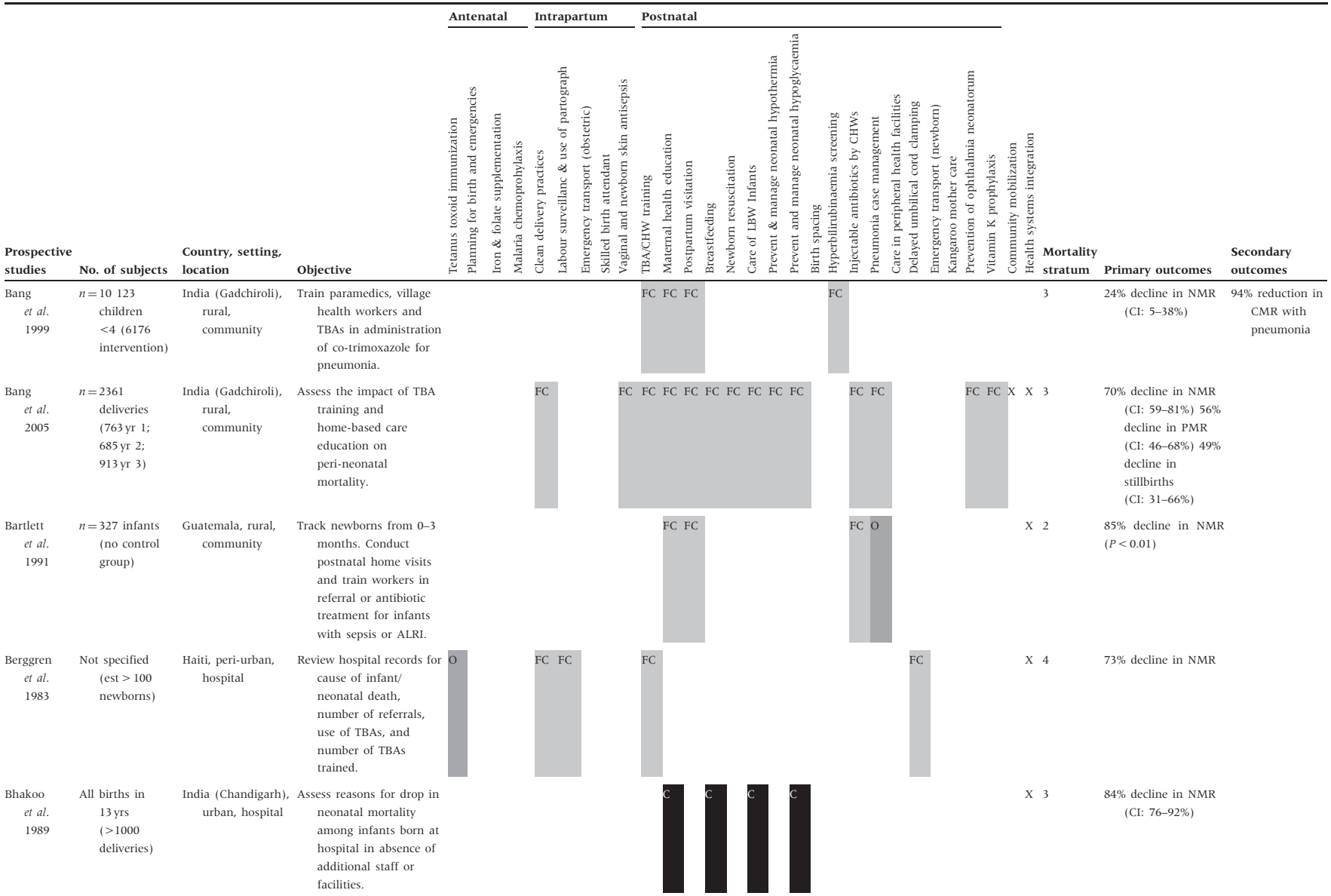
Table 2 Intervention components of packages tested in randomized controlled trials with antenatal interventions only

RCTs (with *only* antenatal interventions)	No. of subjects	Country, setting, location	Objective	Antenatal: Iron & folic acid supplementation	Antenatal: Multiple micronutrient supplementation	Antenatal: Protein-energy supplementation	Antenatal: Zinc supplementation	Antenatal: Vitamin A supplementation	Antenatal: Malaria chemoprophylaxis	Antenatal: Protein supplementation	Community mobilization	Health systems integration	Mortality stratum	Primary outcomes	Secondary outcomes
Bouvier *et al.* 1997	$n = 126$ women	Malawi, rural, community	Cluster-randomize pregnant women to two groups: malaria prophylaxis with proguanil (200 mg/day) or chloroquine (300 mg/week); all women received iron supplementation as well.	(O) only iron					O				3	No data on mortality.	Seasonal variation in birth weight disappeared during intervention.
Caulfield *et al.* 1999	$n = 1295$ women	Peru, urban, hospital	Randomize pregnant women between 10 and 24 wks gestation to receive either iron + folate or zinc supplements in order to evaluate supplements' impact on birth weight.	O			O					X	2	No data on mortality.	No impact of zinc supplement on birth weight, rates of LBW, or prematurity.
Dijkhuizen & Wieringa 2001	$n = 229$ women (4 groups; 38 in I-F control group)	Indonesia, rural, community	Randomize pregnant women 10-20 wks gestation to 1 of 4 groups: beta-carotene supplement, zinc (30 mg/day) supplement; beta-carotene and zinc supplements; and control. All groups also received iron + folate (I-F).	O			O	O					2	No data on mortality.	Increase in mean birth weight of infants.
Fawzi *et al.* 1998	$n = 1075$ HIV+ women (269 Vit A; 269 MVt; 270 MVt & Vit A)	Tanzania, urban, clinic	Randomize HIV-infected women between 12 and 20 wks gestation into 4 groups: daily dose of vitamin A; multivitamins excluding vitamin A; multivitamins including vitamin A; and a placebo control group.		O			O				X	3	No data on mortality.	Risk of LBW decreased by 44%; severe preterm birth declined 39%; risk of SGA fell 43%.

Kumwenda *et al.* 2002	$n = 697$ HIV+ women	Malawi, urban, hospital	Randomize HIV-infected women to receive daily doses of iron-folate alone (control group) or combined with vitamin A from 18-28 weeks gestation until delivery.	O			O				X	3	No data on mortality.	Slight differences in mean birth weight; 42% decrease in infant anaemia at 6 weeks.
Mardones-Santander *et al.* 1988	$n = 597$ women (298 PUR group; 299 V-N group)	South Africa, rural, clinic	Provide pregnant women with powdered milk with high milkfat (PUR) or multiple-micronutrient-fortified powdered milk (V-N).		O	O					X	2	No data on mortality.	Increase in mean birth weight.
Merialdi 2001	$n = 242$ women	Peru, periurban, clinic	Randomize pregnant women between 10 and 16 wks gestation who are already receiving iron and folate supplements to either 25 mg zinc/day or a placebo.	O			O				X	2	No data on mortality.	Positive effect on foetal femur diaphysis growth. No effect on birth weight.
Mora *et al.* 1978	$n = 456$ women	Colombia, Urban	Evaluate 2 groups of pregnant women: those given protein-energy supplements and multiple micronutrients and those given no supplements.		O	O						3	46% decline in NMR; 25% decline in PMR; 75% decline in stillbirths.	
Ndyomugyenyi & Magnussen 2000	$n = 860$ primigravidae (284 CQ; 282 control)	Uganda, rural, clinic	Randomize primigravidae in their first and second trimester to: oral chloroquine (CQ), placebo iron-folate; placebo of all 3 interventions; or oral iron-folate and placebo CQ.	O					O		X	3	No data on mortality.	Significantly reduced frequency of LBW (2%).
Qureshi *et al.* 1973	$n = 126$ women (37 I-F, 39 protein-energy + I-F)	India, rural	Assign pregnant women at 20 wks gestation to 1 of 3 groups: iron-folate (I-F) supplement; iron-folate with dietary supplement; and no supplement (control group).	O		O						3	No data on mortality.	Increased mean birth weight (0.27 and 0.81 kg for groups 1 and 2, respectively, vs. control).
Ramakrishnan *et al.* 2003	$n = 873$ pregnant women	Mexico, semi-rural, community	Recruit pregnant women before 13 wks gestation to receive 1 of 2 supplements (iron or iron + multiple micronutrients) and routine antenatal care.	(O) only iron	O					O		2	No data on mortality.	Mean birth weight and birth length did not significantly differ between the 2 groups.
Ross *et al.* 1985	$n = 171$ nutritionally deficient women	South Africa, rural	Provide pregnant women 20 or more wks gestation with one of: micronutrients and high-bulk supplementation; micronutrients and low-bulk supplementation; zinc; or placebo.		O	O	O					2	No data on mortality.	Increased mean birth weight. No effect on length of gestation.
Total interventions (by intervention type)				**8**	**5**	**4**	**4**	**3**	**2**	**1**				

Notes: Key to service delivery mode: ☐ Family/community (FC); ▒ Outreach (O); ■ Clinical (C).
LBW = low birth weight; RCT = randomized controlled trial; SGA = small for gestational age.

Table 3 Intervention components of packages tested in prospective studies



Prospective studies	No. of subjects	Country, setting, location	Objective	Mortality stratum	Primary outcomes	Secondary outcomes
Bang *et al.* 1999	$n = 10\,123$ children <4 (6176 intervention)	India (Gadchiroli), rural, community	Train paramedics, village health workers and TBAs in administration of co-trimoxazole for pneumonia.	3	24% decline in NMR (CI: 5–38%)	94% reduction in CMR with pneumonia
Bang *et al.* 2005	$n = 2361$ deliveries (763 yr 1; 685 yr 2; 913 yr 3)	India (Gadchiroli), rural, community	Assess the impact of TBA training and home-based care education on peri-neonatal mortality.	3	70% decline in NMR (CI: 59–81%) 56% decline in PMR (CI: 46–68%) 49% decline in stillbirths (CI: 31–66%)	
Bartlett *et al.* 1991	$n = 327$ infants (no control group)	Guatemala, rural, community	Track newborns from 0–3 months. Conduct postnatal home visits and train workers in referral or antibiotic treatment for infants with sepsis or ALRI.	2	85% decline in NMR ($P < 0.01$)	
Berggren *et al.* 1983	Not specified (est > 100 newborns)	Haiti, peri-urban, hospital	Review hospital records for cause of infant/ neonatal death, number of referrals, use of TBAs, and number of TBAs trained.	4	73% decline in NMR	
Bhakoo *et al.* 1989	All births in 13 yrs (>1000 deliveries)	India (Chandigarh), urban, hospital	Assess reasons for drop in neonatal mortality among infants born at hospital in absence of additional staff or facilities.	3	84% decline in NMR (CI: 76–92%)	

Borulkar *et al.* 1998	$n=2266$ at-risk infants (all neonates admitted)	India (Dahanu), peri-urban, hospital	Examine effects of horizontal programming by recording treatments and interventions for at-risk infants over 5-year period.													C	C		C	C					C		C		X	3	No comparison group.
Bose *et al.* 1999	$n=175$ newborns (all neonates admitted)	India (Kaniyambadi), rural/peri-urban, hospital	Evaluate outcome of infants admitted to secondary care to determine if LBW can be managed without specialist intervention.														C	FC	C			C								3	No comparison group.
Daga & Daga 1989; Daga *et al.* 1992; Daga *et al.* 1993; Daga *et al.* 1996	$n=333$ infants	India (Bombay), urban, hospital	Assess the impact of warm rooms, being fed mother's milk, mother's participation in neonatal care and minimal interventions on survival outcomes.										C		C	C		C	C											3	30% decline in NMR 58% decline in PMR
Deorari *et al.* 2000	Not clear (all births in participating hospitals in 15 month period)	India, urban/peri-urban, hospital	Assess the impact of National Resuscitation Programme (trained health care workers and training equipment for neonatal resuscitation).										C				C												X	3	No significant NMR change.
Dutt & Srinivasa 1997	$n=356$ live births	India (Pondicherry), rural, community	Determine impact of MCH services on child survival by tracking health outcomes and care received in first 5 years.	O		O				O			FC	O	FC						O					O			X	3	15% decline in NMR over historical average.
Greenwood *et al.* 1990	$n=1913$ women (673 baseline)	The Gambia, rural, community	Train TBAs in antenatal care, malarial prophylaxis, risk assessment and referral, clean delivery, and neonatal care.	O	FC		O	FC					O															X		3	33% decline in NMR (CI: 2–54%)
Kapoor *et al.* 1991	Unknown	India (Ballabgarh), rural, community	Provide tetanus toxoid immunization to pregnant women (1970) and distribute clean delivery kits to mothers (1982).	O				FC						FC																3	58% decline in NMR

(continued)

Table 3 Continued

				Antenatal				Intrapartum					Postnatal																						
Prospective studies	**No. of subjects**	**Country, setting, location**	**Objective**	Tetanus toxoid immunization	Planning for birth and emergencies	Iron & folate supplementation	Malaria chemoprohylaxis	Clean delivery practices	Labour surveillanc & use of partograph	Emergency transport (obstetric)	Skilled birth attendant	Vaginal and newborn skin antisepsis	TBA/CHW training	Maternal health education	Postpartum visitation	Breastfeeding	Newborn resuscitation	Care of LBW Infants	Prevent & manage neonatal hypothermia	Prevent and manage neonatal hypoglycaemia	Birth spacing	Hyperbilirubinaemia screening	Injectable antibiotics by CHWs	Pneumonia case management	Care in peripheral health facilities	Delayed umbilical cord clamping	Emergency transport (newborn)	Kangaroo mother care	Prevention of ophthalmia neonatorum	Vitamin K prophylaxis	Community mobilization	Health systems integration	**Mortality stratum**	**Primary outcomes**	**Secondary outcomes**
Kumar 1995	$n = 2041$ births (968 control)	India, rural	Train TBAs in basic newborn resuscitation vs. mucus extraction and bag-and-mask ventilation.										FC				FC																3	19% decline in PMR	
Meegan *et al*. 2001	$n = 118\,160$ births (88 471 control)	Kenya/Tanzania, rural, community	Supply TBAs with delivery kits and train in clean delivery, antenatal, intrapartum and postnatal care.					FC					FC	FC	FC																X		2 (Ken.) 3 (Tanz)	84% decline in NMR (0.75/1000, range 0–3 vs. 82/1000, range 74–93)	
O'Rourke *et al*. 1998	$n = 409$ women	Bolivia, rural, community	Evaluate impact of women's groups diagnosing, designing, implementing, and evaluating community-based solutions to maternal and perinatal health problems.		FC			FC			O		FC	FC		FC				FC	FC										X		2	63% decline in PMR (CI: 27–56%)	25% increase in breastfeeding rates (25.3% pre to 50.3% post)
Pratinidhi *et al*. 1986	$n = 851$ at-risk infants	India, rural	Train CHWs in risk identification and referral, resuscitation, newborn care, and education of mothers through home visits.					FC					FC	FC	FC	FC	FC	FC	FC	FC											X		3	27% decline in NMR (CI: 0–53%)	
Total interventions (by intervention type)				**4**	**2**	**1**	**1**	**7**	**1**	**1**	**1**	**1**	**11**	**9**	**7**	**6**	**6**	**5**	**5**	**5**	**2**	**2**	**2**	**2**	**1**	**1**	**1**	**1**	**1**	**1**					

Notes: Key to service delivery mode: Family/community (FC); Outreach (O); Clinical (C).

ALRI = acute lower respiratory tract infection; CHW = community health worker; CI = confidence interval; CMR = child mortality rate; LBW = low birth weight; MCH = maternal and child health; NMR = neonatal mortality rate; PMR = perinatal mortality rate; TBA = traditional birth attendant.

Table 4 Intervention components of packages tested in retrospective studies and quasi-experimental trials

				Antenatal					Intra-partum			Postnatal															
Retrospective studies	**No. of subjects**	**Country, setting, location**	**Objective**	Antenatal care package	Detect & manage breech, multiple births	Iron & folic acid supplementation	Multiple micronutrient supplementation	Pregnancy-induced hypertension	Clean delivery practices	Labour surveillance & use of partograph	Assisted vaginal delivery	TBA/CHW training	Postpartum visitation	Breastfeeding	Prevent & manage hypoglycaemia	Newborn resuscitation	Care of LBW infants	Birth spacing	Care in peripheral health facilities	Hyperbilirubinaemia screening	Emergency transport (newborn)	Vitamin K prophylaxis	Community mobilization	Health systems integration	**Mortality stratum**	**Primary outcomes**	**Secondary outcomes**
Atukorala *et al.* 1994	$n = 195$ pregnant women	Sri Lanka, rural, community	Give pregnant women a fortified food supplement (Thriposha), iron supplements (60 mg/day) or 0.25 mg folate.			O	O																	1	No data on mortality.	No effect on birth weight.
Datta *et al.* 1987	$n = 410$ LBW infants (211 control)	India (Haryana), rural, community	Assess the feasibility of introducing a case management programme for acute respiratory infections among LBW infants at the primary health care level.									O	O				O		O				X		3	24% decline in IMR (CI: 6–35%)	Reduced duration of infections; 66% decline in infection case fatality rate.
Janowitz *et al.* 1988	$n = 1961$ women who gave birth	Bolivia, hospital	Collect data from a random sample of postpartum women to compare outcomes of deliveries attended by family members, TBAs, and hospital staff.						FC	FC		FC	FC												2	Hospital-born newborns 4 times less likely to die than newborns referred after complications.	No data.
Smith *et al.* 2000	$n = 1961$ TBA clients (932 controls)	Ghana, rural, community	Give TBAs kit and training on normal pregnancy & newborn care, referral, family planning, feeding, and immunization.	FC					FC	FC		FC	FC	FC	FC	FC	FC	FC			FC		X	X	3	No difference in PMR.	100% increase in antenatal TT referrals (25% pre vs. 58% post).
van der Mei 1994	$n = 567$ LBW infants	Ghana, rural, hospital	Train mothers and nurses in basic newborn care in a limited-resource environment.						C					C	C	C				C		C	X	3	No comparison group.	
Yan 1989	7 out of 29 townships	China, rural, hospital	Develop risk approach based on existing three-tiered (village, township and county) Maternal Child Health Network.	C	C			C			C	O											X	2	34% decline in NMR (CI: 0–34%)	
Total interventions (by type of intervention)				**2**	**1**	**1**	**1**	**1**	**3**		**2**	**1**	**4**	**3**	**2**	**2**	**2**	**2**	**1**	**1**	**1**	**1**	**1**				

Notes: Key to service delivery mode: ▭ Family/community (FC); ▭ Outreach (O); ■ Clinical (C).

CHW = community health worker; CI = confidence interval; IMR = infant mortality rate; LBW = low birth weight; NMR = neonatal mortality rate; PMR = perinatal mortality rate; TBA = traditional birth attendant; TT = tetanus toxoid.

Table 5 Studies Testing Packages of Neonatal Health Interventions by Service Delivery Mode and Time Period of Intervention

Service delivery mode	Preconception/Antenatal	Intrapartum	Postnatal	Interventions	Studies*
Facility-based clinical	**Interventions: 3** **Studies: 1**[46] (+) Yan[46] retrospectively looked at antenatal care, detection and management of birth complications (−) No preconception interventions, screening and treatment for syphilis, intermittent presumptive treatment for malaria, or treatment for asymptomatic bacteriuria	**Interventions: 3** **Studies: 3**[8,45,46] (+) Studies examined delivery with skilled attendant and/or clean delivery[45,46] (−) Facility-based clinical interventions limited[45,46] and do not include proven interventions such as emergency obstetric care or corticosteroids for preterm labour	**Interventions: 37** **Studies: 9**[1,6,7,26–33,45] (+) Newborn resuscitation,[1,6,7,26–28,33,45] LBW care[6,26] (−) Only 2 studies included facility-based interventions across multiple time periods,[45,46] limited pneumonia case management[1,7]	**43**	**11**
Outreach	**Interventions: 39** **Studies: 20**[2,7,8,9–21,25,34–36,41] (+) Some TT,[7,25,34–36] malaria chemoprophylaxis,[9,17,35] birth preparedness[2] (−) No preconception interventions, dominant focus on micronutrient supplementation,[10–18,20] folic acid given only *after* conception;[10,11,13,15,17,18,32,39] limited antenatal visits	**Interventions: 4** **Studies: 4**[2,8,34,39] (+) Limited focus on clean delivery,[2] emergency transport,[34] and skilled attendant at birth[39] (−) Limited use of outreach service delivery in the intrapartum period[2,34,39]	**Interventions: 14** **Studies: 8**[2,7,8,24,34,35,42,46] (+) TBA/CHW training,[2,35,42,46] postpartum visitation[7,42] (−) Limited use of outreach service mode delivery for postnatal interventions, limited pneumonia case management[24]	**57**	**25**
Family/community	**Interventions: 10** **Studies: 9**[2,3,4,5,6,8,35,39,44] (+) Some birth preparedness[5,6,35] (−) No preconception interventions, limited use of family/community service delivery mode	**Interventions: 13** **Studies: 12**[5–7,23,25,35,36,38–40,43,44] (+) Clean delivery[5–7,23,25,35,36,38–40,43,44] (−) Predominant focus on clean delivery	**Interventions: 72** **Studies: 20**[2,3,4,5,6–8,22–25,28,34,36–40,43,44] (+) Breastfeeding,[5,23,39,40,44] thermal care,[5,6,23,27,28] LBW care,[5,23,28,40,44] maternal education,[2,3,22–24,34,36,38–40] and postpartum visits[2,3,5,6,7,22–24,34,38,40] (−) Limited pneumonia case management,[22] emergency transport for obstetric/neonatal complications,[6,34] KMC,[5] and skin care[5]	**95**	**21**
Interventions	**52**	**20**	**123**	**195**	
Studies*	**27**	**17**	**29**		**41**

*Totals do not equal sum of columns or rows due to presence of multiple intervention types in a single study (double counting).

(+) Strengths of research; (−) Limitations of research.

CHW = community health worker; KMC = Kangaroo mother care; LBW = low birth weight; TBA = traditional birth attendant; TT = tetanus toxoid.

[1]Arif and Arif (1999); [2]Jokhio *et al*. (2005); [3]Kielmann *et al*. (1978a); [4]Kielmann *et al*. (1978b); [5]Kumar *et al*. (2004); [6]Manandhar *et al*. (2004); [7]Rahman (1982); [8]Srinivasan *et al*. (1995); [9]Bouvier *et al*. (1997); [10]Caulfield *et al*. (1999); [11]Dijkhuizen and Wieringa (2001); [12]Fawzi *et al*. (1998); [13]Kumwenda *et al*. (2002); [14]Mardones-Santander *et al*. (1988); [15]Merialdi (2001); [16]Mora *et al*. (1978); [17]Ndyomugyenyi and Magnussen (2000); [18]Qureshi *et al*. (1973); [19]Ramakrishnan *et al*. (1999); [20]Ramakrishnan *et al*. (2003); [21]Ross *et al*. (1985); [22]Bang *et al*. (1999); [23]Bang *et al*. (2005); [24]Bartlett *et al*. (1991); [25]Berggren *et al*. (1983); [26]Bhakoo *et al*. (1989); [27]Borulkar *et al*. (1998); [28]Bose *et al*. (1999); [29]Daga and Daga (1989); [30]Daga *et al*. (1993); [31]Daga *et al*. (1992); [32]Daga *et al*. (1996); [33]Deorari *et al*. (2000); [34]Dutt and Srinivasa (1997); [35]Greenwood *et al*. (1990); [36]Kapoor *et al*. (1991); [37]Kumar (1995); [38]Meegan *et al*. (2001); [39]O'Rourke *et al*. (1998); [40]Pratinidhi *et al*. (1986); [41]Atukorala *et al*. (1994); [42]Datta *et al*. (1987); [43]Janowitz *et al*. (1988); [44]Smith *et al*. (2000); [45]van der Mei (1994); [46]Yan (1989).

components, clean delivery was the only intrapartum intervention in six of the eight prospective studies and three of the four retrospective studies. Six studies packaged clean delivery training for birth attendants with tetanus toxoid immunization (Kielmann *et al*. 1978a; Rahman 1982; Berggren *et al*. 1983; Greenwood *et al*. 1990; Kapoor *et al*. 1991; Srinivasan *et al*. 1995), and three studies provided labour surveillance in addition to clean delivery (Berggren *et al*. 1983; Janowitz *et al*. 1988; Smith *et al*. 2000), but none of these used a partograph.

Overall, postnatal interventions ($n = 123$) were more common components of packages than antenatal ($n = 52$) or intrapartum ($n = 20$) interventions (Table 5). Common postnatal interventions included TBA/CHW training ($n = 21$; notably, their activities often spanned the antenatal-intrapartum-postnatal continuum), postnatal visitation, maternal health education, breastfeeding promotion, newborn resuscitation, care of LBW infants, and hypothermia prevention and management. Very few studies included more technically involved but efficacious postnatal interventions such as newborn resuscitation or injectable antibiotics for neonatal infections.

Packaging patterns versus existing recommendations

Commonly bundled interventions included TBA/CHW training and postpartum visitation, implemented together in 12 studies; eight of these also included maternal health education (Tables 1, 3). Training CHWs was the most common strategy to provide neonatal resuscitation ($n = 5$), diagnose and refer or treat pneumonia cases ($n = 6$) and provide breastfeeding advice ($n = 5$). During the antenatal period, interventions appeared bundled out of convenience of administration, and no clear patterns defined the overall packaging of supplements or immunizations.

Only one study (Bang *et al*. 2005) implemented the complete family-community package of evidence-based essential newborn care interventions described in *The Lancet's* Neonatal Survival Series (Darmstadt *et al*. 2005). Bang *et al*. reported a 70% decline in the neonatal mortality rate (NMR), a 56% decline in the perinatal mortality rate (PMR), and a 49% decline in the stillbirth rate. A community-based study by Manandhar *et al*. (2004) did not implement a designated package of interventions but instead educated women's groups about proven interventions using pictorial cards, allowing each group to select the package of interventions they wanted to implement. Although only a small fraction of the population was involved in women's groups, the intervention led to a 30% decline in the NMR, suggesting successful community mobilization and communication of messages outside of the group meetings. These studies incorporating the full range of family-community interventions were among those with the greatest impact on primary outcomes (Table 6). Five others approached the family-community package ideal, implementing packages missing just one or two of the recommended interventions (Kielmann *et al*. 1978a; Rahman 1982; Daga *et al*. 1996; Arif and Arif 1999; Kumar *et al*. 2004).

Only one study approximated *The Lancet*-recommended antenatal package of outreach-based interventions (Srinivasan *et al*. 1995), though it lacked breastfeeding outreach. Most studies lacked intrapartum interventions other than clean delivery. However, several studies provided packages of interventions closely corresponding to recommendations for care of LBW infants (Rahman 1982; Pratinidhi *et al*. 1986; Datta *et al*. 1987; Bhakoo *et al*. 1989; Daga *et al*. 1996; Arif and Arif 1999; Bang *et al*. 1999; Bose *et al*. 1999; Smith *et al*. 2000; Kumar *et al*. 2004); case management of pneumonia (Kielmann *et al*. 1978a; Rahman 1982; Bartlett *et al*. 1991; Arif and Arif 1999; Bang *et al*. 1999); and emergency neonatal care (Pratinidhi *et al*. 1986; Borulkar *et al*. 1998; Bang *et al*. 1999; Bose *et al*. 1999; Smith *et al*. 2000; Manandhar *et al*. 2004). Notably, emergency care in these studies rarely conformed to the recommended model of prompt referral of outborn infants with complications to facilities; in many settings, this model was infeasible because of economic or geographic barriers to access care, lack of quality care in local facilities, and/or cultural traditions to protect vulnerable newborns by keeping them at home for some time after birth. No study offered any of the situational or additional interventions recommended by *The Lancet's* series, including periconceptual folic acid supplementation, intermittent presumptive treatment for malaria, detection and treatment of asymptomatic bacteriuria, and corticosteroids for preterm labour. Several intervention packages recommended by *The Lancet's* series were also missing: none of the studies included the emergency obstetric care package, the skilled maternal and immediate newborn care package, or the antenatal care III package, which includes tetanus toxoid as well as syphilis screening and treatment in addition to taking a pregnant woman's medical history and providing a complete physical examination to screen for complications.

Table 6 Impact of interventions on neonatal and perinatal mortality by service delivery mode

	Impact	
Service delivery mode	NMR	PMR
ALL	72% ($n = 1$)	–
Clinical only	0–84% ($n = 2$)	
Outreach only	30–46% ($n = 3$)	28–53% ($n = 2$)
Family-community only	19–84% ($n = 5$)	41–56% ($n = 2$)
Family-community AND Outreach	15–85% ($n = 6$)	30–63% ($n = 2$)
Clinical AND Family-community	No data ($n = 1$)	
Clinical AND Outreach	0–34% ($n = 2$)	

NMR = neonatal mortality rate; PMR = perinatal mortality rate.

Community mobilization and participatory methods

More than a quarter (11/41) of the reviewed studies included community mobilization components (Web Table 1). Among studies without community mobilization components, there were examples of significant formative research with community members (Meegan *et al*. 2001) and community members as intervention implementers (Dutt and Srinivasa 1997). Specific activities constituting 'community mobilization' varied considerably, ranging from community-wide sensitization meetings (Pratinidhi *et al*. 1986; Greenwood *et al*. 1990; Kumar *et al*. 2004; Bang *et al*. 2005) and health education sessions (Datta *et al*. 1987; Bang *et al*. 1994; Bang *et al*. 1999; Kumar *et al*. 2004) to weekly community women's groups run by trained local

facilitators (O'Rourke *et al*. 1998; Manandhar *et al*. 2004). Studies that had community mobilization components generally fell into two categories: (1) older studies offering health education to improve uptake of externally generated interventions (Kielmann *et al*. 1978a; Pratinidhi *et al*. 1986; Datta *et al*. 1987; Greenwood *et al*. 1990), and (2) newer studies adopting participatory research approaches (O'Rourke *et al*. 1998; Bang *et al*. 1999; Smith *et al*. 2000; Manandhar *et al*. 2004). Most studies targeted mothers and fathers, and occasionally neighbours and other community members.

Community mobilization activities were commonly delivered by community members or CHWs (7/11 studies). A family-community service delivery mode was prominent in 10 of these 11 studies, but three also used outreach or clinical-based interventions (Datta *et al*. 1987; Greenwood *et al*. 1990; Manandhar *et al*. 2004). All 11 studies with community mobilization components reported primary outcomes, compared with just 12 of 30 studies that did not employ community mobilization strategies. Several studies with community mobilization activities reported the highest declines in PMR (56–63%) (O'Rourke *et al*. 1998; Bang *et al*. 2005) and NMR (70–84%) (Meegan *et al*. 2001; Bang *et al*. 2005) of all the studies we reviewed. One study lacking a community mobilization component asserted that intervention effectiveness might have been improved by community mobilization activities, particularly maternal education (Rahman 1982).

Care-seeking components and behaviours

Care-seeking components were defined as any behaviour or service that enabled or enhanced the ability of mothers or their neonates to receive skilled medical care during delivery or for obstetric or neonatal complications; 16 of the 41 studies reviewed contained a care-seeking component (Web Table 2). Studies incorporating community mobilization activities were more than twice as likely as other studies to encourage care-seeking activities (6/11 studies with community mobilization activities, versus only 9/30 studies without community mobilization activities). Most studies that included care-seeking components were prospective cohort studies (8/16); antenatal RCTs, predominantly based on outreach activities, uniformly did not include promotion of care-seeking. In two studies, mothers were trained to provide care for their neonates and seek help from medical professionals in case of problems while *within* a hospital environment (Daga *et al*. 1992; Arif and Arif 1999).

Referral procedures were the most commonly promoted form of care-seeking (13 of the 16 studies with care-seeking components included referrals) (Kielmann *et al*. 1978a; Pratinidhi *et al*. 1986; Datta *et al*. 1987; Greenwood *et al*. 1990; Bartlett *et al*. 1991; Srinivasan *et al*. 1995; Bouvier *et al*. 1997; Dutt and Srinivasa 1997; Bang *et al*. 1999; Bose *et al*. 1999; Smith *et al*. 2000; Manandhar *et al*. 2004; Jokhio *et al*. 2005), but were often limited to instructing TBAs, midwives or CHWs about the indications for referral (Berggren *et al*. 1983; Datta *et al*. 1987; Srinivasan *et al*. 1995; Bouvier *et al*. 1997; Bang *et al*. 1999; Bose *et al*. 1999; Smith *et al*. 2000; Jokhio *et al*. 2005). Enhanced follow-through of referral through supportive intervention components was uncommon ($n = 5$ studies), although approaches included creating demand among parents through education (Bang *et al*. 1990; Bartlett *et al*. 1991), providing accompanied referral (Greenwood *et al*. 1990; Bartlett *et al*. 1991), developing a cadre of personnel to link TBAs to the health system (Jokhio *et al*. 2005), ensuring that referred cases were within the capacity of referral centres to handle (Bartlett *et al*. 1991), or strengthening the capacity of health services to handle referred cases (Manandhar *et al*. 2004).

Problems with promotion of care-seeking were noted by several studies. Five studies found parents uncooperative with or unable to pursue recommended referrals (Pratinidhi *et al*. 1986; Datta *et al*. 1987; Srinivasan *et al*. 1995; Bang *et al*. 1999; Bose *et al*. 1999). Pratinidhi *et al*. (1986) noted parents had problems obtaining transportation, while Smith *et al*. (2000) found that TBA care was associated with prolonged labour, suggesting a possible reluctance to refer by TBAs, although this was not confirmed. A meta-analysis of the effectiveness of TBA training on pregnancy outcomes has shown more promising results (Buekens 2003; Sibley and Sipe 2004), but identifying appropriate roles for TBAs during the antenatal, intrapartum and postnatal periods remains a priority research area (Bhutta *et al*. 2005). Datta *et al*. (1987) found that CHWs/TBAs were uncomfortable or inaccurate in their assessments of who needed referral, and Yan (1989) noted possible inability of referral centres to provide quality care, evidenced by high PMRs.

A few studies that did not include care-seeking components remarked that their interventions might have been improved through including education about danger-sign recognition (Kapoor *et al*. 1991; Srinivasan *et al*. 1995), encouraging care-seeking by parents (Rahman 1982), and/or altering typical referral arrangements such as substituting care by nurses (Borulkar *et al*. 1998) or mothers (Bhutta *et al*. 2005) for typical care by paediatricians at referral centres due to scarcity of trained staff, although such approaches to increase care-seeking for childhood illnesses have met with variable success (Kidane and Morrow 2000; Mohan *et al*. 2004).

Health systems and effectiveness trials

Although several studies involved the local health system, none was considered a true effectiveness trial implemented at scale in a health systems setting (Web Table 3). Less than one-quarter of all studies reviewed engaged any part of the health system and even fewer considered sustainability issues; no study was fully integrated into the health system. Ten studies utilized one or more components of the existing health system to deliver some of the interventions in the package, (Arif and Arif 1999; Bang *et al*. 1999; Bartlett *et al*. 1991; Borulkar *et al*. 1998; Deorari *et al*. 2000; Rahman 1982; Smith *et al*. 2000; Srinivasan *et al*. 1995; van der Mei *et al*. 1994; Yan 1989), including involving local staff and/or facilities or collaborating with the health system and international non-governmental organizations.

Ten additional studies involved health systems to a lesser degree. Two prospective studies (Bhakoo *et al*. 1989; Dutt and Srinivasa 1997) used hospital records for baseline and retrospective analyses. Six studies used the existing health system

only to identify study participants (Mardones-Santander *et al*. 1988; Fawzi *et al*. 1998; Caulfield *et al*. 1999; Ndyomugyenyi and Magnussen 2000; Merialdi 2001; Kumwenda *et al*. 2002), and two studies (Berggren *et al*. 1983; Bang *et al*. 1993) attempted to involve referrals to the existing health system but were either unsuccessful or had unintended consequences. Bang *et al*. (1993) found that few patients referred for severe pneumonia sought follow-up care, while Berggren *et al*. (1983) observed that having midwives refer patients for obstetric complications and cord care overburdened health facilities.

Public versus private providers in intervention delivery

Of the 41 studies, private providers alone were most commonly used to deliver interventions (16/41) (Web Table 4), but public providers (11/41), as well as a combination of public and private providers (14/41), were also common. Providers at the community level, most commonly TBAs and/or CHWs, were instrumental in delivering interventions in 22 studies; TBAs/CHWs were involved in 17/40 studies and were the principal intervention implementers in half of these studies. These TBAs/CHWs were predominantly private providers (and most commonly, independent community members rather than trained NGO staff); TBAs/CHWs were clearly affiliated with government programmes in only three studies (Greenwood *et al*. 1990; Srinivasan *et al*. 1995; Dutt and Srinivasa 1997), and in one of these cases, most TBA trainees had practiced privately before the programme began (Greenwood *et al*. 1990). TBAs/CHWs were almost universally involved in RCTs that included postnatal interventions (5/6 studies) (Kielmann *et al*. 1978b; Rahman 1982; Srinivasan *et al*. 1995; Kumar *et al*. 2004; Manandhar *et al*. 2004; Jokhio *et al*. 2005). By contrast, TBAs were rarely used in antenatal RCTs to deliver interventions, but one study trained private village health workers (CHWs) to distribute supplements (Dijkhuizen and Wieringa 2001). Antenatal micronutrient supplementation RCTs in rural community settings, often characterized by poorly functioning government health infrastructure, were conducted using predominantly private providers, i.e. study staff (Qureshi *et al*. 1973; Ross *et al*. 1985; Bouvier *et al*. 1997; Dijkhuizen and Wieringa 2001; Ramakrishnan *et al*. 2003); in areas with a more developed health infrastructure, studies tended to enlist the help of public providers (hospital or antenatal clinic staff) to recruit participants or to distribute supplements (Mardones-Santander *et al*. 1988; Caulfield *et al*. 1999; Ndyomugyenyi and Magnussen 2000; Merialdi 2001; Kumwenda *et al*. 2002). Studies with a prospective design were most likely to use a combination of public and private providers, accounting for 8 of 14 such studies.

Outcome reporting

Twenty-eight studies reported primary outcomes and 23 reported secondary outcomes; 7 and 14 RCTs reported primary and secondary outcomes, respectively (Table 1). In some cases, study sample size limited researchers' ability to report statistically significant findings. While many studies reported declines in perinatal and neonatal mortality, the association between particular interventions or sub-packages of interventions and primary outcomes was impossible to ascertain from available data. In almost all studies where primary outcomes were reported, these figures reflected the aggregate impact of the packaged interventions; measured or estimated effects attributable to individual component interventions or sub-packages were not reported. Only one study, by Rahman (1982), presented disaggregated results for TBA training and tetanus toxoid immunization, but its phased study design precluded computation of the impact of the packaged interventions.

Of the 23 studies reporting primary outcomes, 20 found moderate to sizeable declines in mortality rates (15–84% reduction) and three reported no change in mortality (Deorari *et al*. 2000; Smith *et al*. 2000). Eight studies reported declines in neonatal mortality that exceeded 50% (Rahman 1982; Berggren *et al*. 1983; Bhakoo *et al*. 1989; Bartlett *et al*. 1991; Kapoor *et al*. 1991; Bang *et al*. 1999; Meegan *et al*. 2001; Kumar *et al*. 2004".). In almost all of these studies, dramatic decreases in tetanus cases appeared to contribute substantially to the reduction in mortality, as three-quarters included tetanus toxoid immunization and/or clean delivery, and all but one were conducted in countries with a mortality stratum of 3 (NMR = 30–45 per 1000 live births) or 4 (NMR >45 per 1000), characterized by incomplete tetanus toxoid immunization and a significant proportion of deaths from tetanus neonatorum. When multiple service delivery modes were used, particularly if family-community interventions were delivered, the mortality impact appeared marginally higher than with single service delivery modes (Table 6).

Studies taking a more holistic approach to packaging interventions (>5 interventions, spanning multiple time periods; $n = 11$) were more likely to report mortality rates (9 of 11 studies) than more targeted studies ($\leq$5 interventions, generally in a single time period; $n = 30$) (12 of 30). However, the range of mortality reduction was comparable; PMR reductions of holistic studies ranged from 29–63% (mean: 45%, median: 41%) compared with 25–58% (mean: 42%, median: 40%) among targeted studies, and NMR reductions ranged from 15–72% (mean: 38%, median: 30%) among holistic studies compared with 0–85% (mean: 54%, median: 48%) among targeted studies. Outcome ranges for holistic studies were also similar in magnitude to studies that employed community mobilization activities, which reported declines in PMR of 0–63% (mean: 35%, median: 41%), and declines in NMR of 27–84% (mean: 31%, median: 42%). This is in large part because studies including community mobilization activities were more likely to be holistic (5/9) than studies without such activities (6/32). Unfortunately, the number of studies was too small, and the array of interventions each offered too varied, to perform appropriate statistical comparisons of holistic and non-holistic studies.

Cost-effectiveness

While some recent studies have modelled cost-effectiveness data for neonatal health interventions (Adam *et al*. 2005; Darmstadt *et al*. 2005), empirical cost-effectiveness data are scarce. Cost-effectiveness data were reported by only two studies implementing neonatal intervention packages (Bang *et al*. 1999; Manandhar *et al*. 2004). In rural India, a complete package of home-based antenatal, intrapartum and postnatal

care (Bang *et al*. 1999), including home visits to provide health education, manage birth asphyxia, care for LBW/preterm babies, prevent and treat hypothermia, and diagnose and treat sepsis, cost US$5.30 per newborn, including $1.30 in non-recurring costs and $3.80 in recurring costs, much lower than the cost of hospital care for newborns in India (Modi and Kirubakaran 1995; Shanmugasandaram *et al*. 1998) and equally effective, at a cost of $95 per life saved. An RCT investigating the impact of facilitating women's groups to implement essential newborn care practices on neonatal health outcomes in rural Nepal (Manandhar *et al*. 2004) reported that the cost per newborn life saved was US$3442 ($4397 including costs of health-service strengthening activities). The intervention cost $111 per year of life saved ($142 including costs of health-service strengthening activities).

Discussion

The empirical evidence evaluating packaged neonatal interventions is most substantial for antenatal outreach (primarily micronutrient supplementation) and postnatal family-community interventions, and weakest for intrapartum family-community and intrapartum and postnatal clinical interventions. Care across the continuum of time periods and across multiple service modes was conspicuously absent in most studies, as were linkages between community and facility-based care and effectiveness trials within health systems. Integration of care among private and public providers was also lacking. The small number of package studies and their failure to incorporate key evidence-based interventions and packages supports assertions from prior reviews that data on packaged interventions remains a significant research gap (Bhutta *et al*. 2005; Darmstadt *et al*. 2005). Thus, key questions remain regarding the feasibility of delivering packages of neonatal interventions, particularly at the community level, as TBAs and CHWs may be limited in their ability to provide multiple interventions, and delivering packages of interventions can require, or be perceived to require, intensified logistical coordination and resource inputs that may be challenging in some low-resource settings.

Very few RCTs examined the impact of intervention packages on neonatal health outcomes (Tables 1, 2). Similarly, differences in study design, varying combinations of interventions and lack of cause-specific mortality data precluded a meta-analysis to project the impact of specific packages on neonatal mortality. Reasons for the dearth of RCTs and rigorous prospective studies on the impact of intervention packages likely include lack of donor support, resource and technical limitations, ethical considerations and, for RCTs, the logistical, financial and analytical challenges associated with factorial designs.

Recommendations and reality

Notably, all of the reviewed studies neglected to include key interventions known to be efficacious and/or cost-effective, including periconceptual folic acid supplementation, syphilis screening and treatment, particularly in sub-Saharan Africa, intermittent presumptive treatment for malaria, antibiotics for asymptomatic bacteriuria, corticosteroids for preterm labour and antibiotics for PPROM (older studies conducted prior to the development of an efficacy and cost-effectiveness evidence base are exempt from this criticism). This may be due, at least in part, to the fact that a number of these interventions require advanced health systems infrastructure (i.e. 'additional' interventions such as detection and treatment of bacteriuria, corticosteroids for preterm labour and antibiotics for PPROM) or strong outreach services (e.g. periconceptual folic acid supplementation, intermittent presumptive treatment for malaria). Only two packages attempted to ensure skilled attendance at birth, despite Safe Motherhood guidelines (Srinivasan *et al*. 1995; O'Rourke *et al*. 1998). Only one study implemented the full family-community package of evidence-based essential newborn care (Bang *et al*. 2005), and only one offered a near-complete antenatal outreach package (Srinivasan *et al*. 1995). While many studies conformed to recommended postnatal packages, there were no examples of complete (or near-complete) intrapartum packages, a significant gap in the evidence base and a missed programmatic opportunity to save maternal and newborn lives. Few studies demonstrated continuity of care through the antenatal, intrapartum and postnatal periods (Darmstadt *et al*. 2005).

Conversely, some studies employed at least one intervention for which evidence of maternal or neonatal benefit is insufficient (Bhutta *et al*. 2005). For example, three incorporated hyperbilirubinemia screening, although the incidence of kernicterus in these settings is not unusually high (Bang *et al*. 1990; van der Mei 1994; Bose *et al*. 1999), suggesting a lack of focus on life-saving interventions.

Potential impact on neonatal mortality

The Lancet's Neonatal Survival Series projected that reductions in neonatal mortality achievable through outreach and family-community services alone range from 18–37% (Darmstadt *et al*. 2005). Although a meta-analysis was not possible, empirical evidence suggests that this estimate may be conservative, at least under conditions testing efficacy. Particularly in countries with high incidence of tetanus neonatorum, the empirical evidence suggests that including tetanus toxoid immunization and clean delivery in packages can dramatically reduce neonatal deaths from tetanus and sepsis (Rahman 1982; Berggren *et al*. 1983; Kapoor *et al*. 1991; O'Rourke *et al*. 1998; Bang *et al*. 1999; Meegan *et al*. 2001), lending support to *The Lancet's* recommendation that outreach services during initial programme implementation in areas with high tetanus incidence and weak health systems may be strategic (Figure 1).

Intentional packaging

The concept of evidence-based neonatal care packages is relatively new, and thus many studies qualifying as packages of interventions here may not have been originally conceived of as packages. Many interventions appear to have been bundled primarily out of logistical convenience, donor directives, organizational expertise or specific lines of scientific inquiry rather than consideration of delivery mode, biological or behavioural synergy, or cost-effectiveness (Victora *et al*. 2004b). Still, opportunistic implementation of interventions

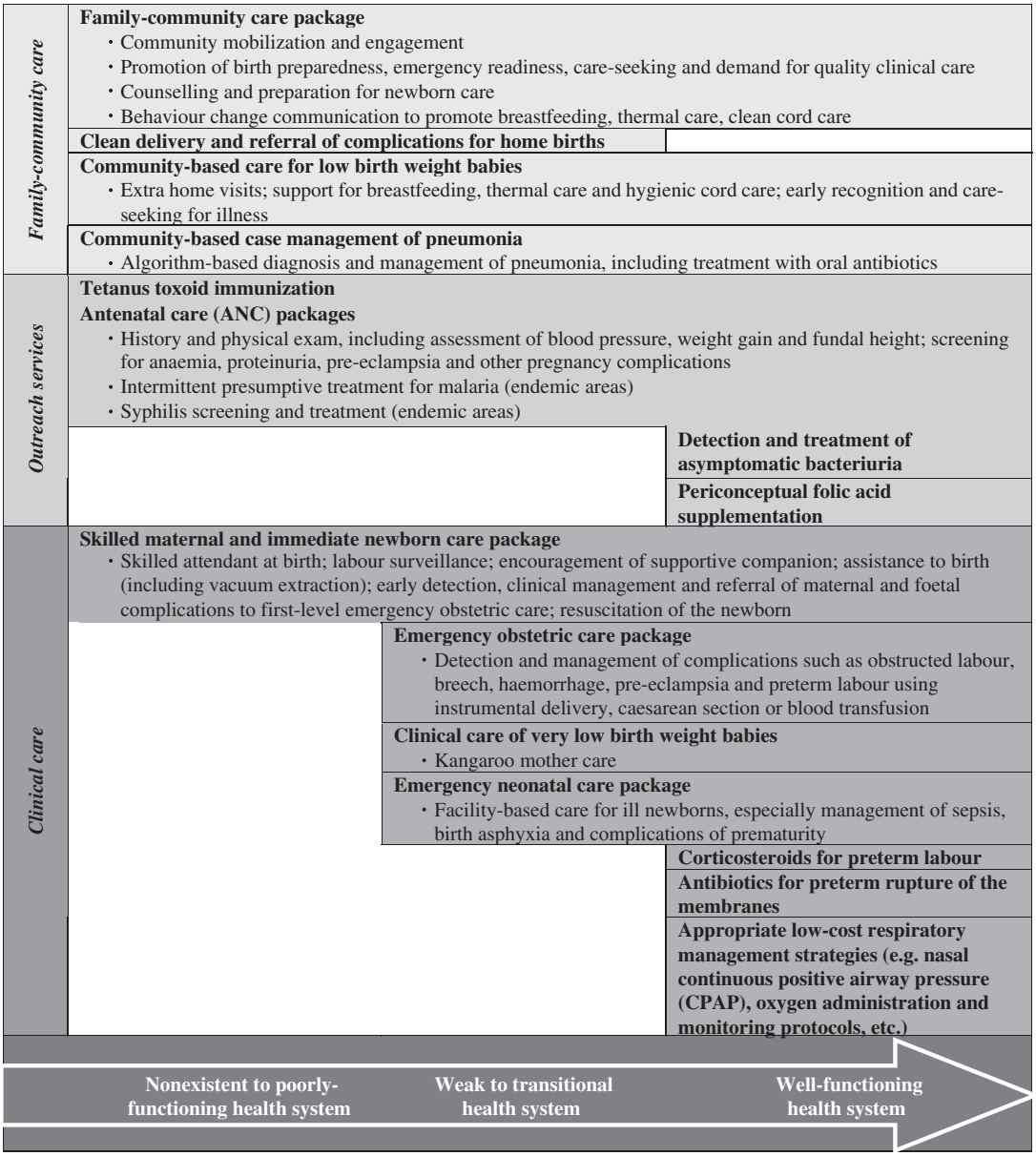


Figure 1 Interventions and intervention packages by service delivery mode and health system capacity

may be an effective initial approach to achieving impact while building a functional health system. Overall, this review suggests that the impact of packages of interventions on health outcomes could likely be improved through a more rational approach to the implementation of cost-effectively and synergistically bundled evidence-based interventions.

Tailoring packages to health systems and regions

Significant geographic and cultural diversity between regions and countries, as well as differences in health system capacity (Box 1, Figure 1), must be considered in intervention design and scaling-up to the national level. Local patterns of health behaviours, prevalence of diseases and outcomes, and service availability should determine components of intervention packages; impact of a package in one setting will not necessarily translate to another. Also, a synergistic benefit of packaged interventions is not assured, as benefit can be diminished by compromised delivery performance from poor training or lack of supervision, deficiencies in supply systems, and selection of interventions poorly matched to the public health needs of a population.

From a health systems perspective, the reviewed studies showed few linkages between family-community interventions and the existing health care infrastructure, although a few studies effectively spanned these service delivery modes as well as outreach (Rahman 1982; Srinivasan *et al*. 1995; Manandhar *et al*. 2004) and created some linkages between communities,

TBAs and facilities (Bartlett *et al*. 1991; Srinivasan *et al*. 1995; Dutt and Srinivasa 1997; Manandhar *et al*. 2004). However, as noted in the analysis of care-seeking components, few studies employed comprehensive efforts to not only identify and refer obstetric and/or neonatal complications, but also to minimize parental refusal, overcome barriers to transferring patients, and ensure facilities had the capacity to handle these referrals. More such studies that develop new ways to build, strengthen and evaluate these linkages can generate data useful for health systems strengthening.

Designing interventions tailored to specific contexts is critical for scalability, sustainability and equity (Victora *et al*. 2004b). Regional differences in health systems and general infrastructure, differences in prevalence of syphilis, malaria and tetanus, and differential rates of perinatal and maternal outcomes (e.g. obstructed labour, LBW and mortality) suggest that packages of evidence-based interventions must be tailored to specific contexts to maximize impact. For example, of 15 studies conducted where malaria and/or syphilis were endemic, only three provided malaria chemoprophylaxis (Greenwood *et al*. 1990; Bouvier *et al*. 1997; Ndyomugyenyi and Magnussen 2000) and none provided syphilis screening and treatment. The capacity of the existing health system must also be considered in selecting intervention components for inclusion in packages; some interventions—particularly clinical interventions requiring advanced diagnostic or treatment strategies, such as diagnosis and treatment of asymptomatic bacteriuria, or use of antenatal antibiotics or intrapartum corticosteroids—could be infeasible in the absence of a well-functioning health system (Figure 1). We reviewed only packages delivered in developing countries, so few of the interventions in these packages were delivered by trained doctors, illustrating and partially explaining the scarcity of clinical interventions in these packages. Lack of integration of community-based care with facility-based care is also apparent.

Implications of packages data for health systems research

Among the reviewed studies, the lack of rigorous effectiveness data—data from trials making wide use of existing human and material resources in health systems and documenting external inputs including costs—is a key research gap. The majority of the RCTs we identified were antenatal, outreach-based micronutrient supplementation trials conducted in carefully selected, controlled environments and heavily dependent on external inputs of financial, human and material resources, i.e. they were efficacy trials. While some studies we reviewed were conducted in more realistic settings, none had sufficient rigour to extract accurate effectiveness data.

Victora *et al*. (2004b) distinguished between intervention efficacy and service delivery mode, arguing that efficacy trials use methods of service delivery that maximize the likelihood of a positive outcome. As none of the studies we identified were true effectiveness trials, Victora's distinction suggests that conducting such trials will require consideration of existing resources, use of multiple service delivery modes, and greater collaboration with health systems to avoid biasing effectiveness measurements.

Packaging of behavioural and technical interventions during the intrapartum and postnatal periods was lacking. To reduce neonatal mortality, a more holistic approach is needed that packages technical interventions within a broader context of behaviour change communications and community mobilization activities, where possible.

Community mobilization as enhancer of effectiveness

This review illustrates the value of community mobilization and empowerment in creating a context in which multiple other health interventions can be effectively provided (Kumar *et al*. 2004; Manandhar *et al*. 2004). Those studies that were concerned with community mobilization and empowerment appeared to provide fertile ground for facilitating the uptake of other interventions, even more technically oriented interventions. Frequent deployment of private community members as intervention providers in the absence of community mobilization activities (Rahman 1982; Berggren *et al*. 1983; Pratinidhi *et al*. 1986; Janowitz *et al*. 1988; Bhakoo *et al*. 1989; Bartlett *et al*. 1991; Kapoor *et al*. 1991; Daga *et al*. 1992; Daga *et al*. 1993; Daga *et al*. 1996; Bouvier *et al*. 1997; Bose *et al*. 1999; Smith *et al*. 2000) appears to reflect missed opportunities to enhance the effectiveness of interventions. As studies with community mobilization components had some of the highest documented impacts on NMR and PMR, community mobilization activities themselves may function to enhance the level of effectiveness of component interventions, a contention that requires further evaluation.

When implemented, documentation of community mobilization activities is typically poor, and standardized approaches to monitoring and measuring coverage and impact, and to describing the implementation and evaluation process, are not yet available. Because community mobilization, particularly participatory approaches, can enhance uptake, effectiveness and sustainability of a broad range of interventions (Rifkin 1990; Rifkin 1996; Morgan 2001), innovative strategies to quantify its impact on primary and secondary outcomes are needed.

Cost-effectiveness

Cost-effectiveness data are crucial to select and bundle interventions suitable for scaling up and to tailor interventions to available health systems resources, but empirical cost-effectiveness data are scarce. The two studies that did include cost-effectiveness analyses were both conducted in rural areas of South Asia, and their costing methods and estimates varied widely (Box 2). While cost-effectiveness analyses are rare throughout the public health literature, especially among developing country studies, such data are necessary to test the implicit assumption that bundling interventions by like service delivery mode is cost-effective. Cost-effectiveness of packaged interventions is a priority research area; researchers could facilitate cost-effectiveness meta-analyses by collecting cost-effectiveness data in a uniform manner and including the data in study results.

Box 3 Research gaps

- Delivery of family-community interventions during the periconceptual period, including folic acid supplementation.
- Intrapartum and postnatal clinical interventions.
- Integration of intervention packages across time periods (i.e. continuum of care from periconceptual through postnatal) and service delivery modes (i.e. family-community, outreach and facility-based clinical care).
- RCT and rigorous prospective study designs examining the impact of packages.
- Inclusion of more technical interventions, e.g. newborn resuscitation, injectable antibiotics for serious bacterial infections.
- Disaggregated effect of single interventions within packages and potential synergistic/antagonistic effects of bundling.
- Effectiveness of TBAs/CHWs as providers of family-community packages.
- Linkages between community and facility-based care.
- Role of private providers in antenatal, intrapartum, and postpartum/neonatal care.
- Care-seeking behaviours for obstetric and neonatal complications.
- Empirical cost-effectiveness data for neonatal intervention packages.
- Impact of evidence-based interventions (Box 1) as part of packages.
- Health systems effectiveness trials of intervention packages.
- Effectiveness of scaling up intervention packages.

Conclusions

At present, the empirical evidence for the impact of neonatal health care packages is a weak base on which to build effective programmes (Box 3). An evidence-based approach to packaging interventions is clearly needed but requires substantial investment in high-quality research and programme learning. Intervention packages should employ multiple service delivery modes along the continuum of care spanning the periconceptual to the postnatal periods, and facilitate linkages between communities and available health care facilities. While 14 of the 41 studies in this review incorporated at least one intervention component to encourage these linkages and many encouraged referrals, few studies made the investments necessary to enhance demand creation for care, to improve the likelihood that parents would appropriately recognize complications or accept referrals, to assist with transportation to a facility, or to improve the capacity of health facilities to provide quality care and handle increased demand.

Finally, significant research is needed regarding scaling up the delivery of interventions to large populations (i.e. the national level, or the state level in large countries with diverse populations) and measuring their impact. Care should be taken that efficacy and effectiveness trials are conducted in settings, and using delivery strategies and resources that render scale-up feasible. Effectiveness interventions should foster synergies between programmes, health systems, private providers and community-based workers. Effectiveness trial data can inform new strategies for strengthening health systems and effectively delivering interventions at scale. Another approach to gauge effectiveness, though sometimes logistically and ethically complicated, but particularly advantageous in situations where a non-intervened comparison group is not possible, is the use of step-wedge introduction of packages in cluster-randomized communities to measure impact, which, in a sufficiently large population, could also be used to test different combinations of interventions at the population level.

An analysis of the impact of successful neonatal health interventions at scale, including careful documentation of processes (e.g. project management), is the next logical step in developing evidence-based packages of interventions to save newborn lives.

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