
Child Health Research Foundation
CHRF Prevent Infections, Save Lives
Second Investigators' Meeting
October 2011
Niagara Falls, Canada
anisa

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Aetiology of Neonatal Infection in South Asia

anisa

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CONTENTS

PREFACE

Samir K Saha
Principal Investigator
ANISA

While countries in South Asia are making considerable progress in achieving the 4th Millennium Development Goal, that is, to reduce under-five mortality rates by two-thirds, reaching the finish line remains a challenge for most countries. Slow reductions in neonatal mortality are largely to blame for this. Public health programmes find it difficult to appropriately address the challenges presented by these deaths in the first month of life, which now constitute more than half of the deaths among under-five children in many of the South Asian countries.

These young infants often die within days of birth without ever being to a doctor, leaving behind no clues as to their causes of deaths. This paucity of information is one of the main obstacles to the development of appropriate interventions to reduce neonatal mortality. Infection is often speculated, but we nonetheless cannot identify the causal agents of the infections, making the planning and designing of comprehensive interventions tricky.

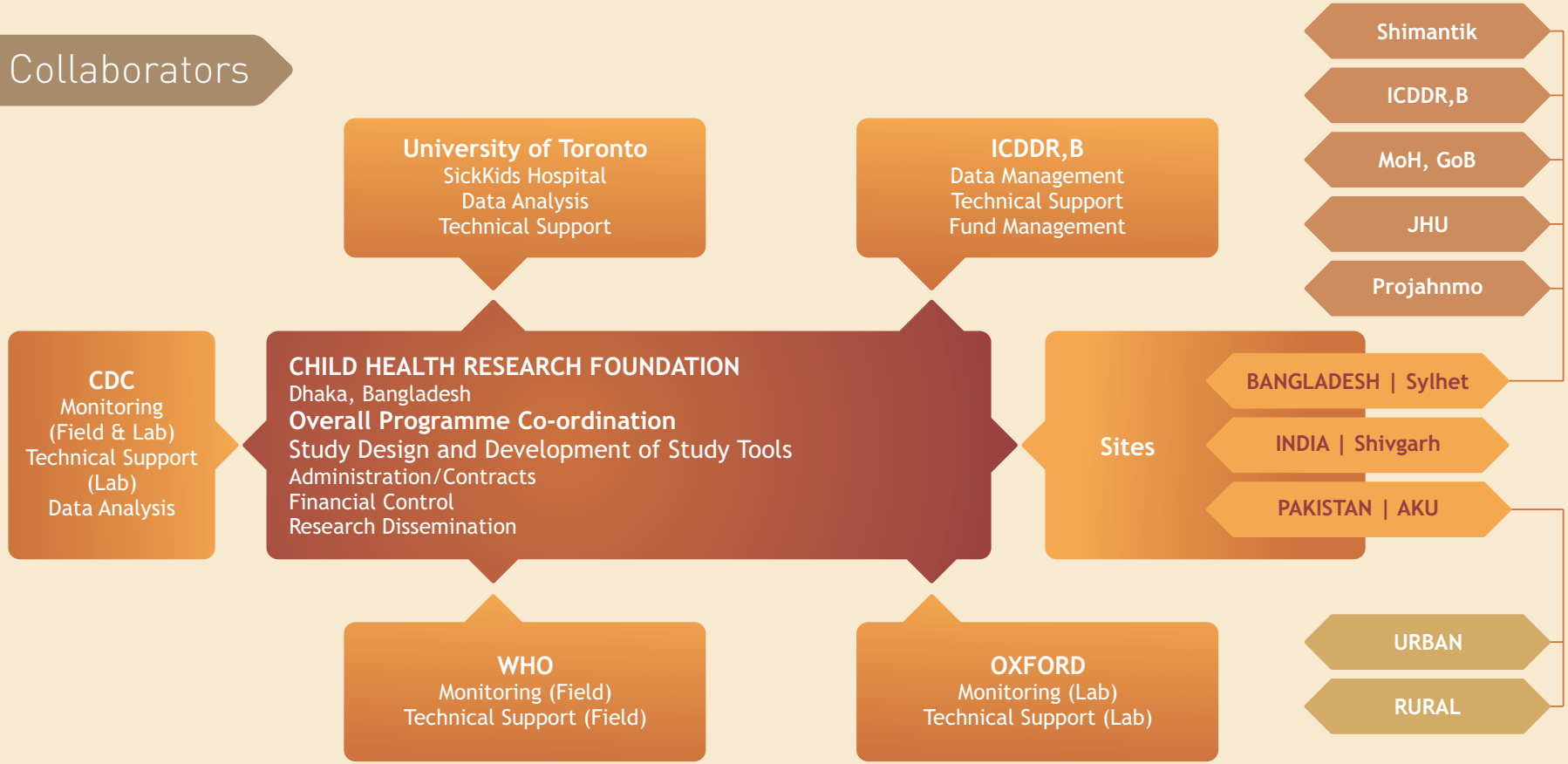
This is where ANISA comes in. It is a rigorous study across 4 community-based sites in Bangladesh, India and Pakistan following mothers through pregnancy and delivery so that the newborns can be monitored from birth. Community health workers are working in many communities in these three countries, assessing the babies immediately after birth at home and then another 9 times until the babies are 2-months old. If any sign of infections are seen in these babies, they are immediately sent to the study facilities where these sick babies are seen by ANISA-trained study doctors who decide whether they meet ANISA eligibility criteria, and provide treatment. Besides saving the lives of numerous neonates, this will enable us to improve our understanding of the aetiology of infections prevalent among neonates in South Asian communities.

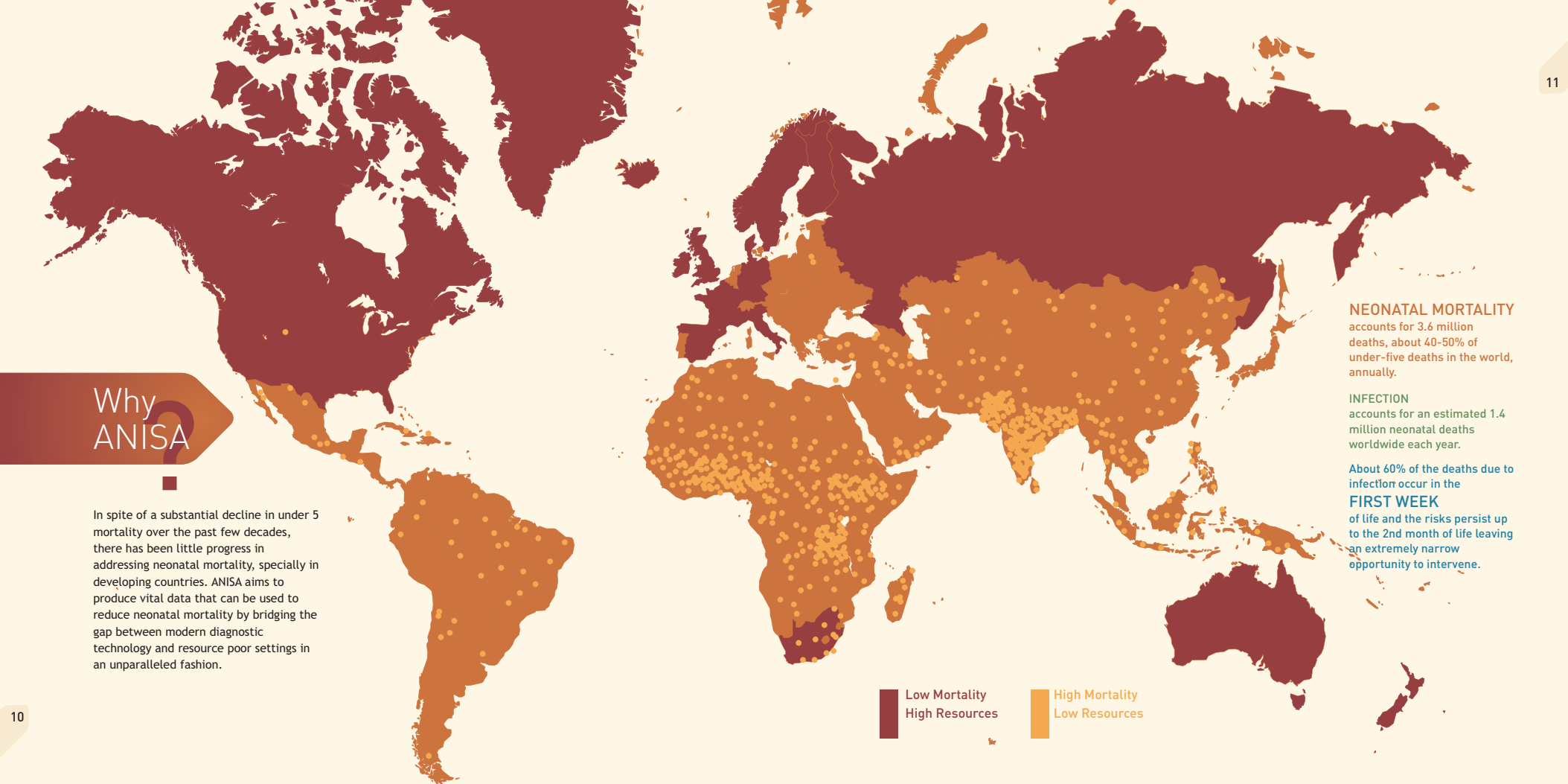
ANISA, for the first time, is also bringing state-of-the-art technologies to the places where they are most needed and challenging the usual scenario of irrational distribution of technologies compared to the burden of ill-health and premature deaths. The extensive knowledge that this study will provide us will guide future treatment policies and help pave the way towards saving the lives of our children.

ANISA
Pleasant Companion

ANISA is being made possible by the collaboration
of different organizations across several countries.
It is this pleasant companionship between multidisciplinary groups
that is vital for the achievement of ANISA goals.

Collaborators





NEONATAL MORTALITY

accounts for 3.6 million deaths, about 40-50% of under-five deaths in the world, annually.

INFECTION

accounts for an estimated 1.4 million neonatal deaths worldwide each year.

About 60% of the deaths due to infection occur in the

FIRST WEEK

of life and the risks persist up to the 2nd month of life leaving an extremely narrow opportunity to intervene.

Why ANISA?

In spite of a substantial decline in under 5 mortality over the past few decades, there has been little progress in addressing neonatal mortality, specially in developing countries. ANISA aims to produce vital data that can be used to reduce neonatal mortality by bridging the gap between modern diagnostic technology and resource poor settings in an unparalleled fashion.

What will ANISA do?

ANISA will determine the causes of neonatal sepsis, their population-based incidence and antibiotic resistance patterns in Bangladesh, India and Pakistan through community-based surveillance by using both standard and cutting edge diagnostic tests. ANISA also aims to identify the risk factors associated with infections and to describe clinical signs of neonatal infections.

and how?
ANISA will ---

1. Conduct population-based surveillance of all pregnancies
2. Identify suspected cases of infections in young infants as early as possible
3. Collect blood, respiratory and/or CSF specimens from suspected cases
4. Determine bacterial aetiology by culture and TaqMan Low Density Array (TLDA)
5. Determine viral aetiology by TLDA
6. Determine antibiotic susceptibility patterns of bacterial isolates
7. Do qualitative controls for all pathogens
8. Maintain strict internal and external quality control and assurance

PREGNANCY SURVEILLANCE

Since most neonates die within days of birth without ever being to a doctor, ANISA aims to intervene in the narrow window of opportunity by monitoring mothers from the start of their pregnancies and determining expected delivery dates. Careful observation of pregnancy also serves to reveal the risk factors associated with neonatal morbidity and mortality

ANISA Community Health Workers (CHWs), with prior informed consent, visit the households of women of reproductive age to identify any new pregnancy. The mothers are offered the standard package of antenatal care available in their respective countries including distribution of iron, folic acid, counseling on immunization, birth preparedness, essential newborn care, and promotion of knowledge about danger signs in both mothers and newborns for appropriate care-seeking. Information is collected to understand the demographics and potential risk factors. All deliveries are reported and a postnatal visit is scheduled as soon as possible within the first 24 hours to ensure detection of danger signs without delay.

SEPSIS SURVEILLANCE

ANISA monitors new born babies for clinical signs indicating infections. Customized CHW-visit-schedule allows prompt detection of signs of neonatal sepsis; at the same time it prevents excessive interventions and overburdening of CHWs and the caregivers. All new born babies are visited within 24 hours and the subsequent surveillance is based on regular, scheduled household visits. CHWs refer sick infants to the nearest designated facilities for physician's evaluation, care and specimen collection. In addition to CHW's referred babies, the physicians at designated ANISA facilities also receive and assess the self-referred cases.

REFERRAL COMPLIANCE

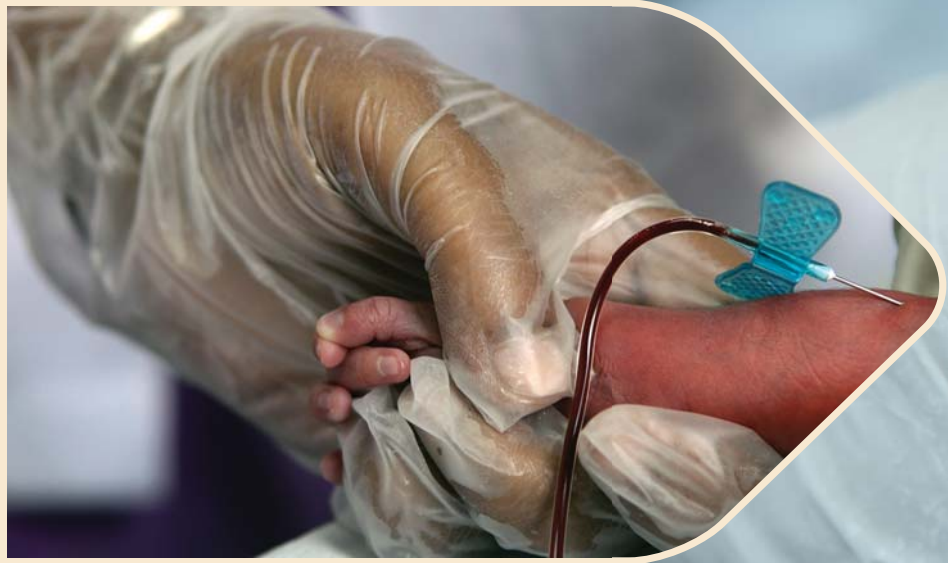
Through their regular visits, the ANISA CHWs build a rapport with the mothers and the community as a whole. Consequently, most of the referrals to the study physicians are complied with, which by itself is one of the indicators of success.

PHYSICIAN'S ASSESSMENT

Designated study physicians assess the referred neonates who are enrolled if upon meeting the ANISA inclusion criteria after informed consent. This is followed by specimen collection briefly before treatment is provided to the infant.

NEONATAL SPECIMEN COLLECTION

After assessment and shortly before treatment, blood, respiratory and, if necessary, CSF specimens are collected from the neonates. This is one of the vital steps in the study and the maintenance of quality in terms of volume and purity is paramount for fulfilling ANISA's goal of revealing aetiology of neonatal infections.



FINDING THE AETIOLOGY

In addition to ensuring good laboratory practice in specimen collection and processing, ANISA has coupled conventional and sophisticated new generation molecular techniques to identify pathogens causing sepsis in newborns. Considering the limited volume of specimens and the possibility of a wide spectrum of infection causing organisms, ANISA has picked up a diagnostic method, TLDA, that can altogether identity 32 different pathogens within a few hours using minimal amount of blood and respiratory specimens.

With the objective of comprehensively covering a wide range of pathogens that commonly cause infections in South Asian newborns, the ANISA Technical Advisory Group has designed specific TaqMan Array Cards for this purpose.

Road Map ANISA

Submission of LOI
April 2009

Submission of full proposal
June 2009

Approval of Proposal
October 2009

Phase 1 Method development
December 2009 to May 2010

Approval of phase 2
July 2010

Obtain IRB with FWA
September 2010

Preparatory activities for field sites
October 2010

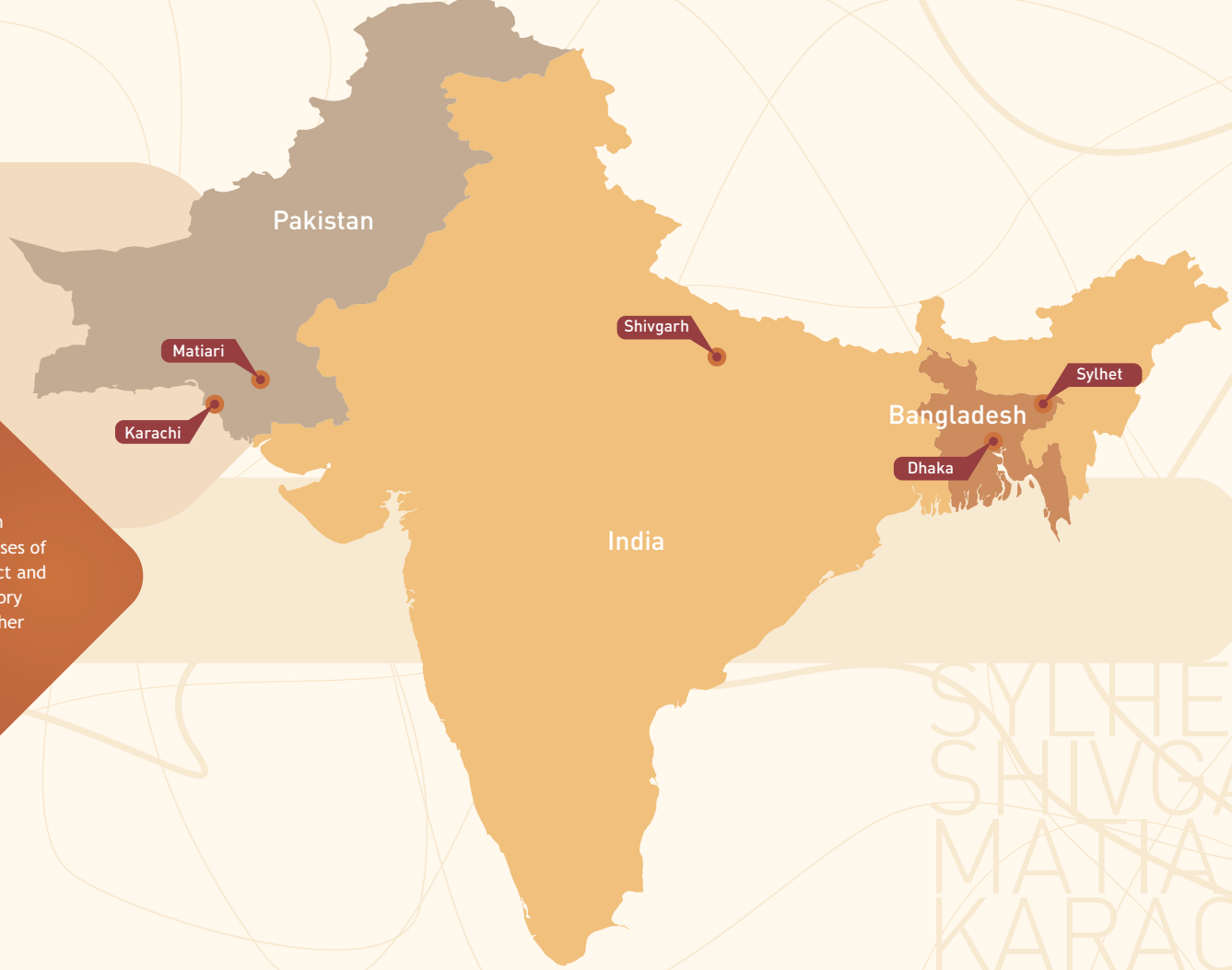
Assessment of site initiation
November 2010

Centralized training
March to June 2011

Initiate Pilot phase
July 2011

Sites at Subcontinent

Sites were selected based on 1) proven track record of conducting community-based surveillance to identify and follow up suspected infection cases, 2) high neonatal mortality, 3) known denominators and potential to yield at least 1000 cases of suspected infections per year, 4) the ability to collect and transport specimens, 5) capacity to conduct laboratory studies and preserve specimens and isolates for further testing and analysis, and 6) willingness to use new diagnostic platforms and participate in external quality control (QC) and quality assurance.



SYLHET
SHIVGARH
MATIARI
KARACHI

Bangladesh
Kanaighat and Zakiganj, Sylhet

Principal Investigator

Dr. Abdullah H. Baqui, Professor of Johns Hopkins Bloomberg School of Public Health, has spent most of his career working to reduce child mortality, particularly in the areas of infection and malnutrition. He has been working in this site for the last 15 years.

Site description

Study area	Kanaighat and Zakiganj
Population of study area	350,000
Birth cohort (over 2 years)	20,000
Neonatal mortality	30/1,000 live births
Number of CHW	One CHW for every 3,000 population (115 CHWs)

Expected Numbers

Neonates with potential infections (10%):
2,000

Enrollment (over 2 years, 70% compliance):
1,400

Bacterial isolates (5% of enrolled neonates):
70

Population based bacterial incidence rate:
3.5/1000 live birth

Viral isolates (30% of enrolled neonates):
420

Population based viral incidence rate:
21/100 live birth

Background

ANISA Bangladesh site is located in the rural areas of Kanaighat and Zakiganj in Sylhet, which is 300 kilometers North-East of capital city Dhaka. This site is run by Projahnmo (Program to Advance the Health of Newborns and Mothers), a partnership programme of Ministry of Health and Family Welfare of Bangladesh, ICDDR,B, Dhaka Shishu Hospital, Child Health Research Foundation, Shimantik and Johns Hopkins University. Projahnmo established Community-based surveillance in this area during 2002 and is still maintaining them through different projects. Specimens from this site will be collected in Government health facilities before being transported to CHRF laboratories in Sylhet and Dhaka for processing.

India
Shivgarh, Uttar Pradesh

Principal Investigator

Dr. Vishwajeet Kumar is a physician with advanced public health training from Johns Hopkins Bloomberg School of Public Health. His scientific work is centred on developing and evaluating innovative models for improving maternal and newborn health. He has been working in this site for last 8 years.

Site description

Study area	Shivgarh
Population of study area	350,000
Birth cohort (over 2 years)	14,000
Neonatal mortality	66/1,000 live births
Number of CHW	One CHW for every 7,000 population

Expected Numbers

Neonates with potential infections (10%)
1400

Enrollment (over 2 years, 70% compliance)
980

Bacterial isolates (5% of enrolled neonates)
49

Population based bacterial incidence rate
3.5/1000 live birth

Viral isolate (30% of enrolled neonates)
294

Population based viral incidence rate
21/100 live birth

Background

ANISA India site is located at Shivgarh village in Uttar Pradesh state which accounts for a quarter of India's neonatal deaths. The Shivgarh site was established in 2003 with support from USAID, N. Delhi Mission, Washington Mission and Saving Newborn Lives Initiative of Save the Children with a grant from the Bill & Melinda Gates Foundation. The Shivgarh site has maintained a Demographic Surveillance System (DSS) along with geo-referenced data points and relational database management system since 2003 which is serving as a reference gold standard for the Bill & Melinda Gates Foundation funded GC13 Health Metrics Project. In this site, specimens will be collected in Government health facilities before being transported to the "Empowerment Lab" at Lucknow for processing.

Pakistan
Urban site - Karachi

Principal Investigator

Dr. Anita Zaidi is Professor and Chair, Department of Paediatrics and Child Health at Aga Khan University (AKU). Dr. Anita's work has focused on neonatal infections, epidemiology of childhood vaccine-preventable illnesses and improving diagnostic and molecular methods of detecting infectious agents in children.

Site description

Study area	Bilal colony, Ibrahim Hyderi Colony, Rehri Goth, Ali Akber Shah Goth and Bhains Colony
Population of study area	270,000
Birth cohort (over 2 years)	19,000
Neonatal mortality	34.4/1,000 live births will update
Number of CHW	One CHW for every 1617 population

Expected Numbers

Neonates with potential infections (8%)
1520

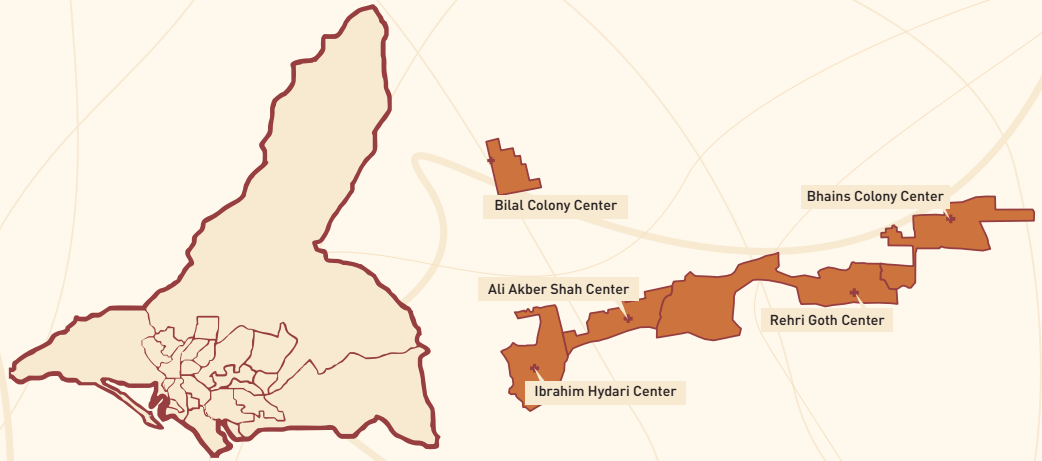
Enrollment (over 2 years, 70% compliance)
1050

Bacterial isolates (5% of enrolled neonates)
59

Population based bacterial incidence rate
3.1/1000 live birth

Number of Viral isolate (30% of enrolled neonates)
315

Population based viral incidence rate
21/100 live birth



Background

ANISA study sites at urban Pakistan are low-income communities with high neonatal mortality rates located in peri-urban coastal fishing villages in Karachi (4 sites) about an hour drive from the Aga Khan University (AKU) campus and one urban squatter settlement (Bilal Colony) at a distance of 30 minutes from AKU. Among them Bilal Colony, Rehri Goth and Ibrahim Hyderi have extensive experience with neonatal research, having served as the only community sites for the Young Infant Clinical Signs Study II. Surveillance for pregnancy and newborn illnesses was established in 2003. All five sites are currently serving as the sites for Saving Newborn Lives (SNL)-sponsored antibiotic therapy trial for neonatal infections (with support from the Bill & Melinda Gates Foundation).

Pakistan
Rural site - Matiari

Principal Investigator

Dr. Zulfiqar A. Bhutta is Noordin-Noor-Mahomed-Sharief Professor and Founding Chair of the Division of Women and Child Health at the Aga Khan University Medical Center. Professor Bhutta has been associated with the Aga Khan University since 1986 and heads a large research team working on issues of maternal, newborn and child survival and nutrition globally and regionally. He is the member of UN Secretary General's Independent Expert Review Group for Maternal and Child Health for achieving MDG targets globally.

Site description

Study area	Matiari
Population of study area	215,199
Birth cohort (over 2 years)	17,000
Neonatal mortality	35/1,000 live births will update
Number of CHW	One CHW for every 12,000 population

Expected Numbers

Neonates with potential infections (10%)
1700

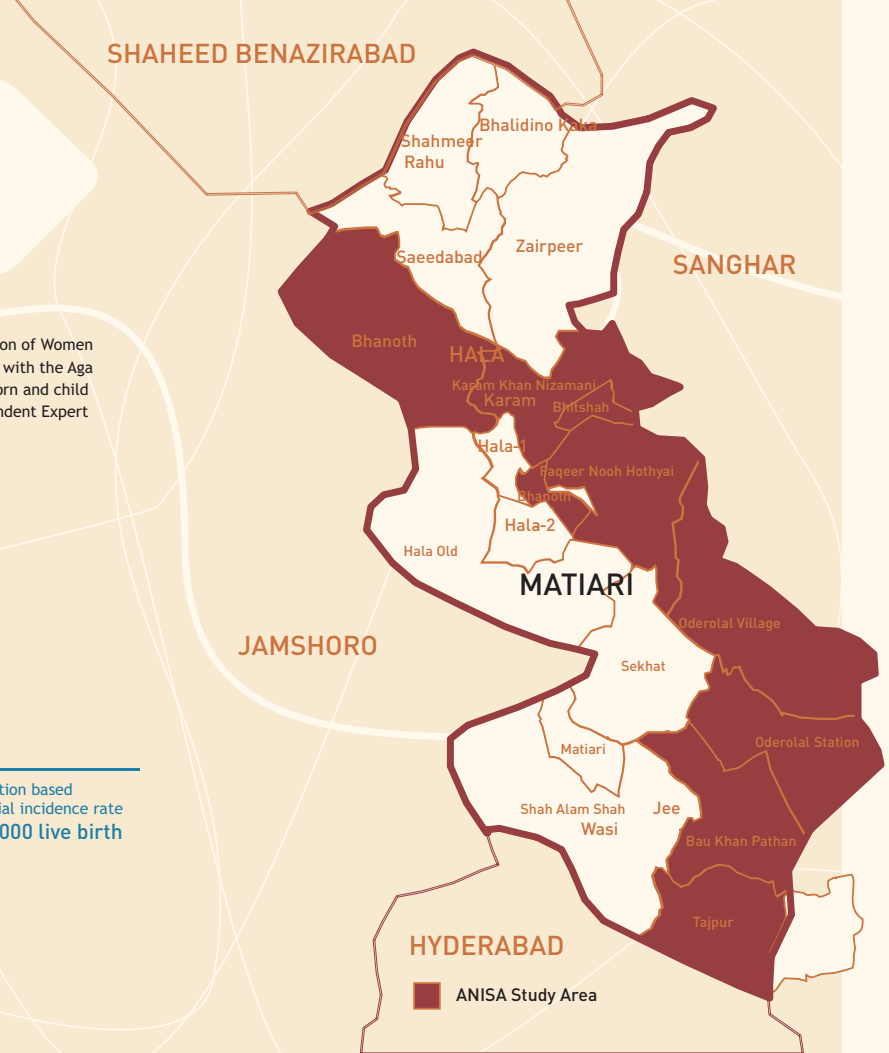
Enrollment (over 2 years, 70% compliance)
1190

Bacterial isolates (5% of enrolled neonates)
60

Population based bacterial incidence rate
3.5/1000 live birth

Number of Viral isolate (30% of enrolled neonates)
357

Population based viral incidence rate
21/100 live birth



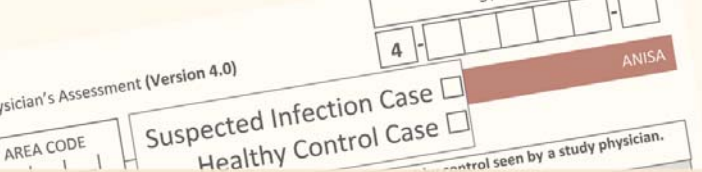
Background

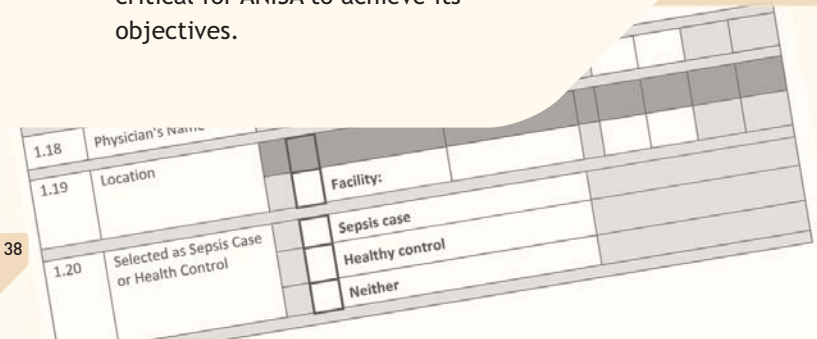
The rural Pakistan site, Matiari, is located 400 kilometers from Karachi. It has developed a prospective cluster randomized trial focusing on the integrated management of birth asphyxia, low birth weight infants and suspected neonatal infections (especially pneumonia) with oral Amoxicillin. This site has experience of conducting multiple community based surveillance and clinical trial funded by NIH, WHO and BMGF. Specimens will be collected at home by experienced medical teams and transported to field lab for blood culture and the rest to AKU lab for molecular tests.

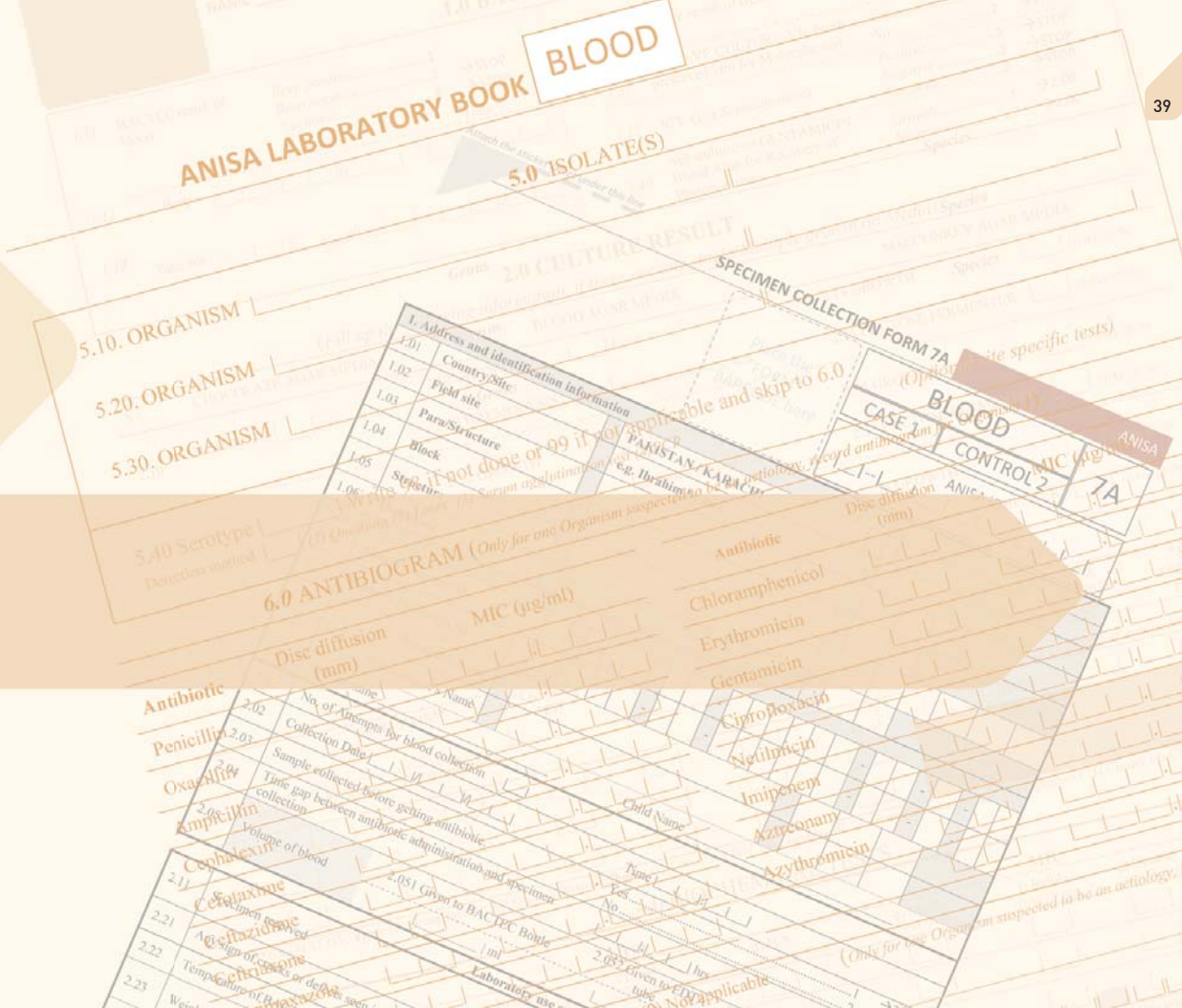
Centralized Management

ANISA
data forms

The ANISA team has worked hard to ensure that data collectors, study physicians, laboratory staff and other study staff in all four sites use the same standardized, easy to use data forms to capture the data critical for ANISA to achieve its objectives.



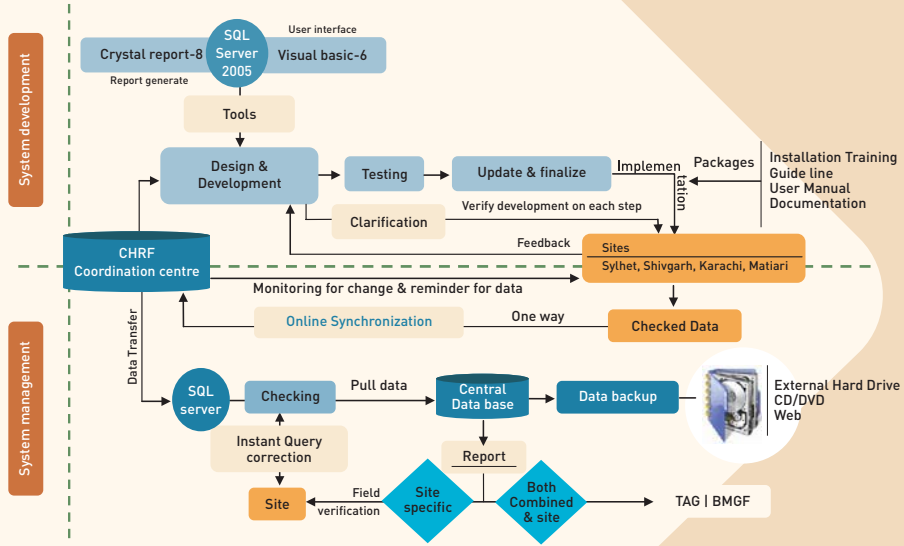




ANISA
data system

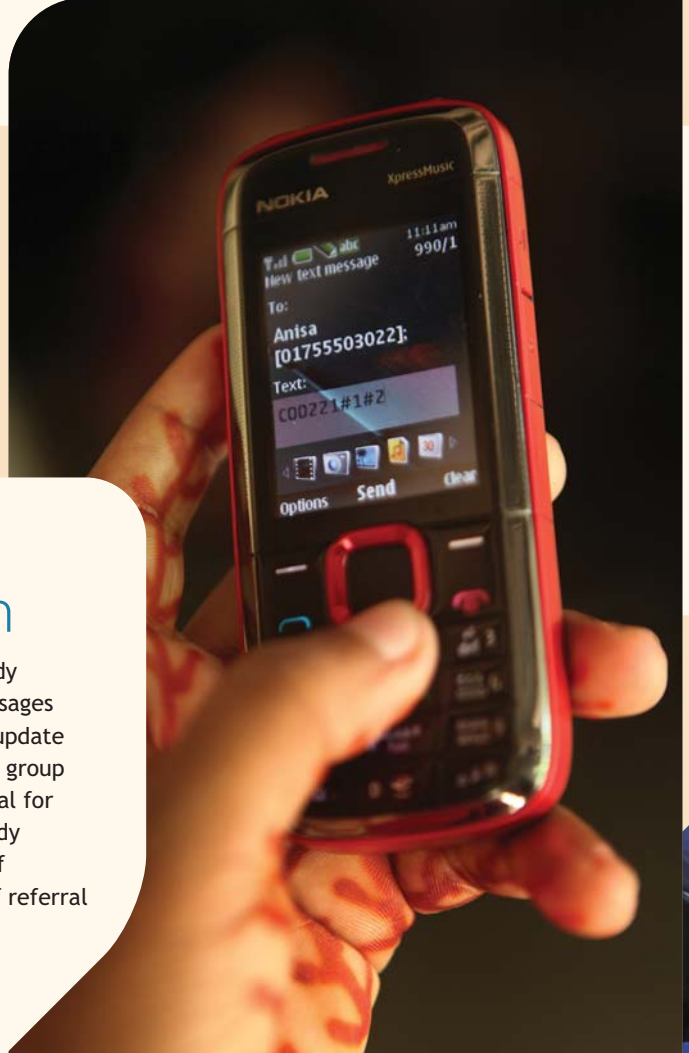
Systems have been designed to transform the paper-based data into electronic data in the form of clean databases accessible to country study teams and also to the ANISA Coordination Team so that analysis can be conducted in real time and progress monitored. The use of paper to record data in the laboratory and to track specimens has been minimized to both avoid errors and ensure that laboratory results are accessible as they become available.

Figure: Development and implementation of data management system coordinated by Data Coordinating centre (CHRF)



SMS System

Data collectors and study physicians use text messages over mobile phones to update the databases on select group key information essential for tracking progress in study enrollment, selection of controls and tracking of referral of sick newborns.



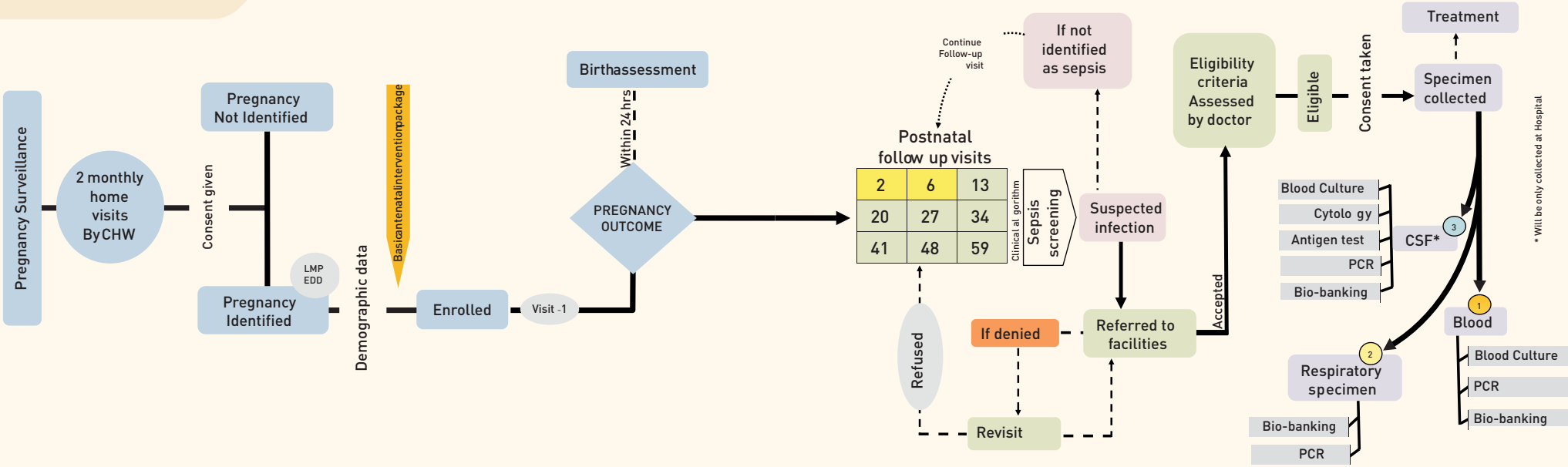
Centralized Training

Harmonization of clinical and laboratory skills, and interpretation of algorithm and laboratory results are pivotal to generate an appropriate set of data from a geographical and culturally diverse population. To achieve these, ANISA team organized centralized training for CHWs, physicians and laboratory staffs.

Centralized Procurement

Similar to centralized training, use of same diagnostic methods, reagents and consumables is also important to generate interpretable results. Keeping that consideration in mind, ANISA ensured similar diagnostic methods at all the sites, and arranged central procurement and shipping of capital equipments and reagents to the sites.

ANISA
Study Profile



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GAUTAM SAHA

CHRF

The Child Health Research Foundation (CHRF) was initiated by a group of child health researchers of Bangladesh, working with a mission to improve child health in Bangladesh and other countries through research and educational efforts to facilitate the decision making on appropriate child health policy. The idea for setting up CHRF came from the realization of the founding group of researchers that developing countries like Bangladesh often lack the evidence needed for rational and timely policy decisions with the consequent inadequate and improper use of limited resources. Scarcity of evidence, in turn, discourages the government and donors to invest in child health. CHRF has established collaboration with different national and international organizations like USAID, WHO, Johns Hopkins University, ICDDR,B, International Vaccine Institute (IVI), Novartis Vaccine Institute of Global Health and others.

In addition to research, the foundation is also making efforts to work with other non-profit hospitals to facilitate low cost diagnostic services for the poor patients with a vision to i) improve child health, and ii) generate evidences for policy decisions.

Through an association with the Department of Microbiology at Dhaka Shishu Hospital and through a consortium of urban and rural hospitals, it has access to research facilities and is able to inform and improve public health approaches and contribute to scientific and medical knowledge and procedures for application in South Asia.

Through these activities Child Heath Research Foundation aims to break the vicious cycle that limits the potential of children in Bangladesh and convert it to a virtuous cycle by making appropriate use of limited resources, produce evidence, facilitate evidence-based policy decisions, shorten the time lag between evidence and implementation and generate interest for increased and sustained investments in child health. Finally, CHRF dreams to contribute in reducing child mortality by creating awareness for appropriate care and care-seeking, ensuring rational treatments, and evidence-based preventive programmes.