Ensuring Quality in Sepsis Study:
DeNIS Collaboration Experience

Structure

I. DeNIS: overview

II. Implementation issues & solutions

III. Quality assurance steps

DeNIS*: Partner institutions

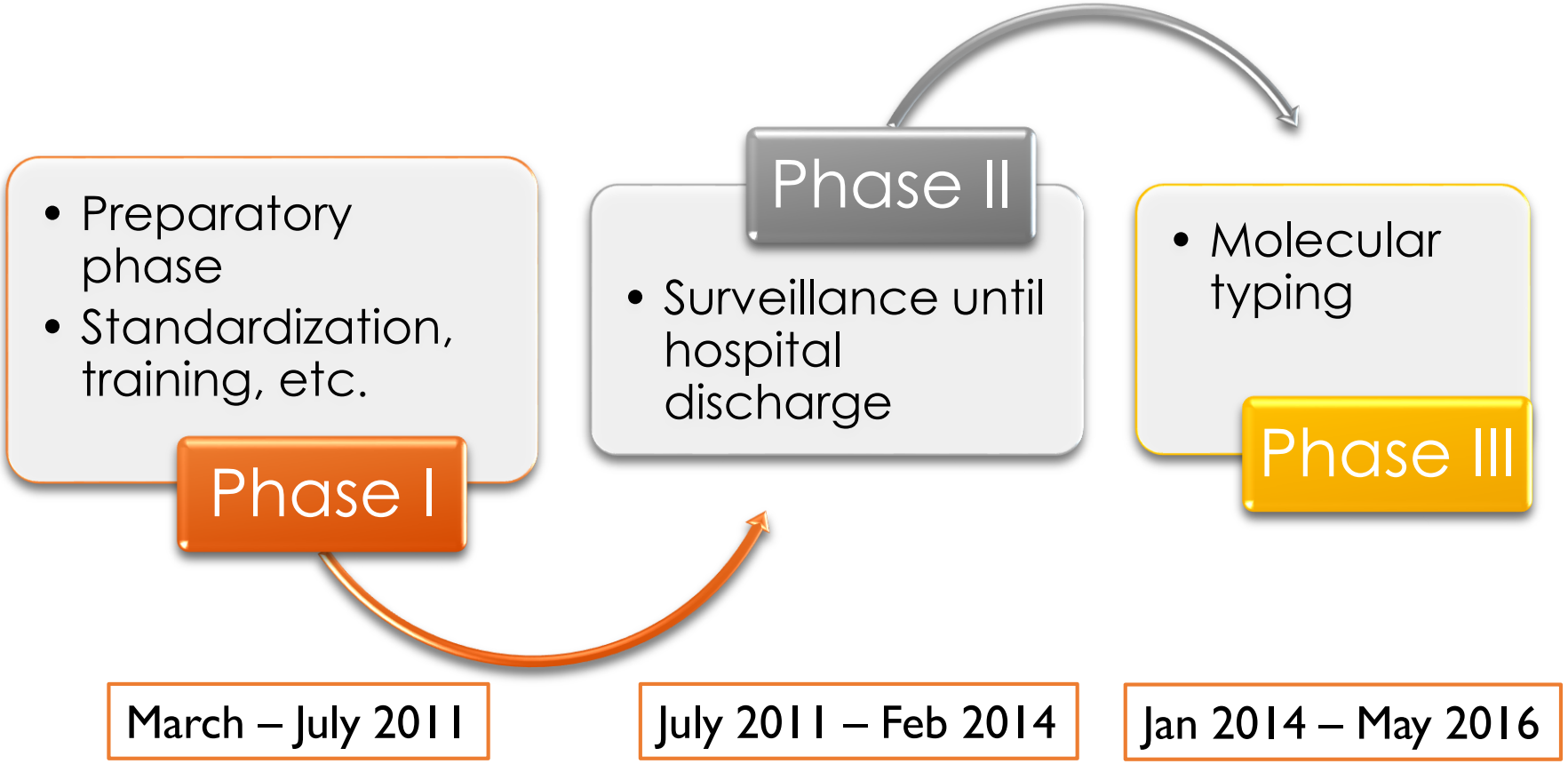
Site	Population	PI (Clinical)	PI (Microbiology)
Chacha Nehru Bal Chikitsalya (CNBC)	***Outborn***	Dr Mamta Jajoo	Dr Vikas Manchanda
Maulana Azad Medical College (MAMC)	***Inborn***	Dr Siddarth Ramji	Dr Krishna Prakash / Dr Surinder Kumar
Safdarjung Hospital		Dr KC Aggarwal / Dr H Chellani	Dr Monorama Deb / Dr R Gaind
AIIMS		Dr VK Paul / Dr AK Deorari	Dr Arti Kapil

**Delhi Neonatal Infection Study (DeNIS) Collaboration*

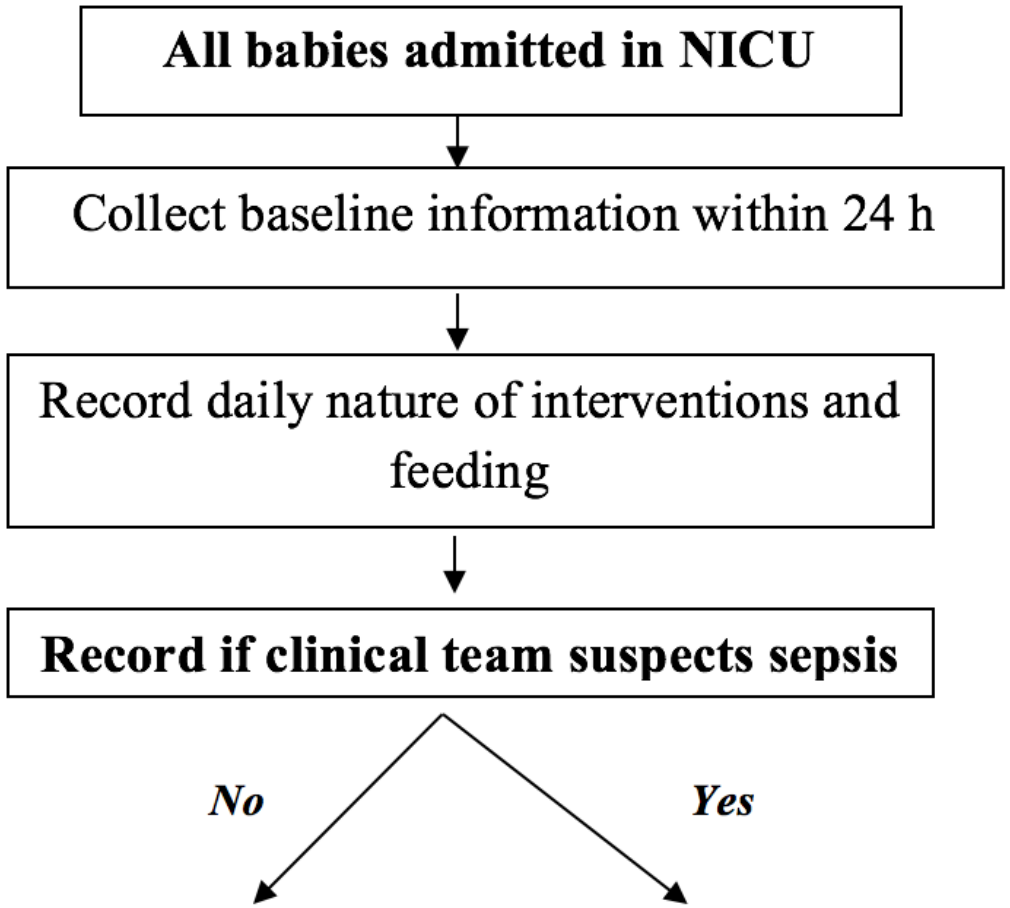
Objectives & outputs

Objectives
To understand the epidemiology of neonatal sepsis
To undertake molecular characterization of common pathogens causing sepsis

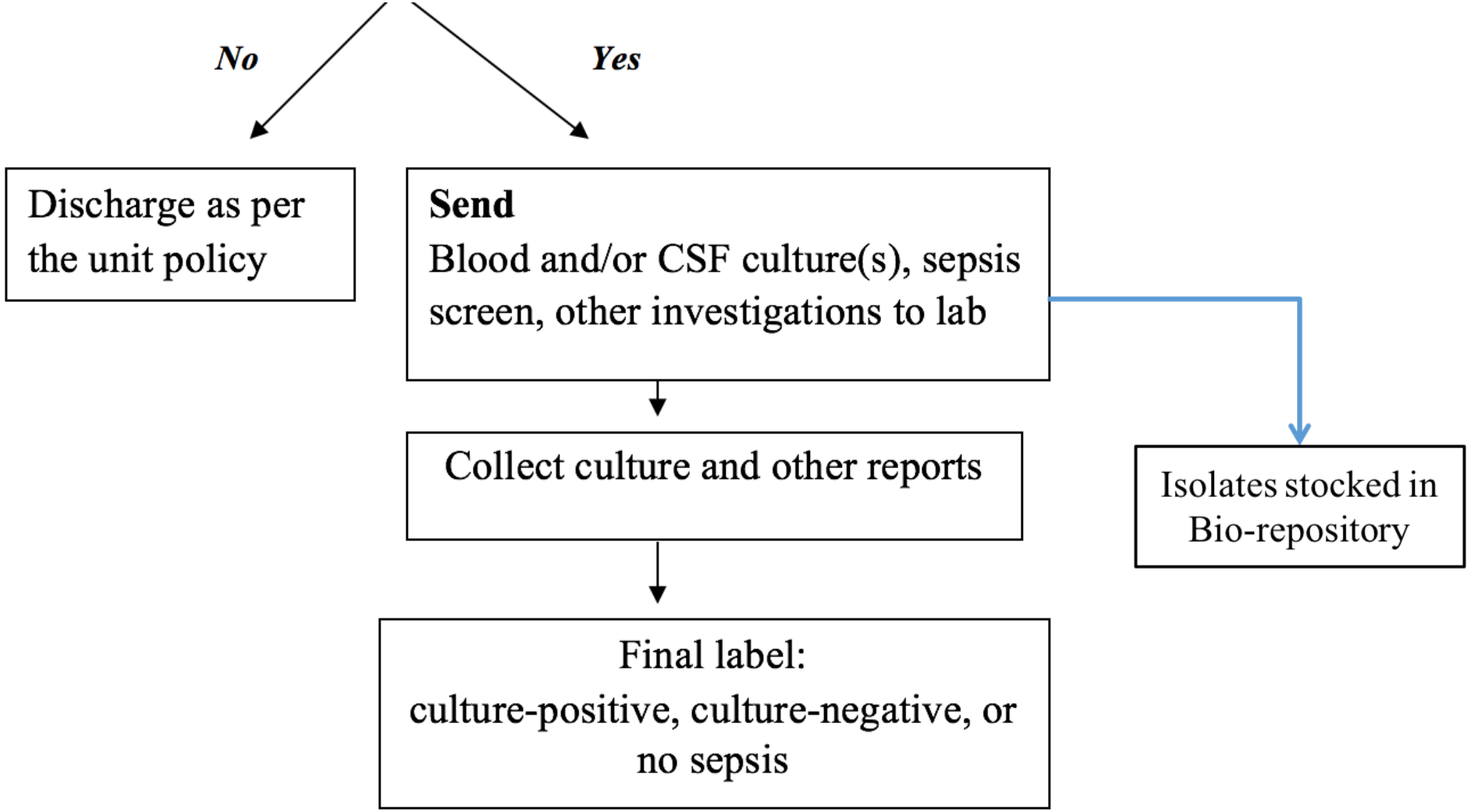
Methods


• Preparatory phase
• Standardization, training, etc.
Phase I
March – July 2011
Phase II
• Surveillance until hospital discharge
July 2011 – Feb 2014
• Molecular typing
Phase III
Jan 2014 – May 2016

Study flow


All babies admitted in NICU
Collect baseline information within 24 h
Record daily nature of interventions and feeding
Record if clinical team suspects sepsis
No
Yes

Study flow…


No
Yes
Discharge as per the unit policy
Send
Blood and/or CSF culture(s), sepsis screen, other investigations to lab
Collect culture and other reports
Isolates stocked in Bio-repository
Final label:
culture-positive, culture-negative, or no sepsis

Methods

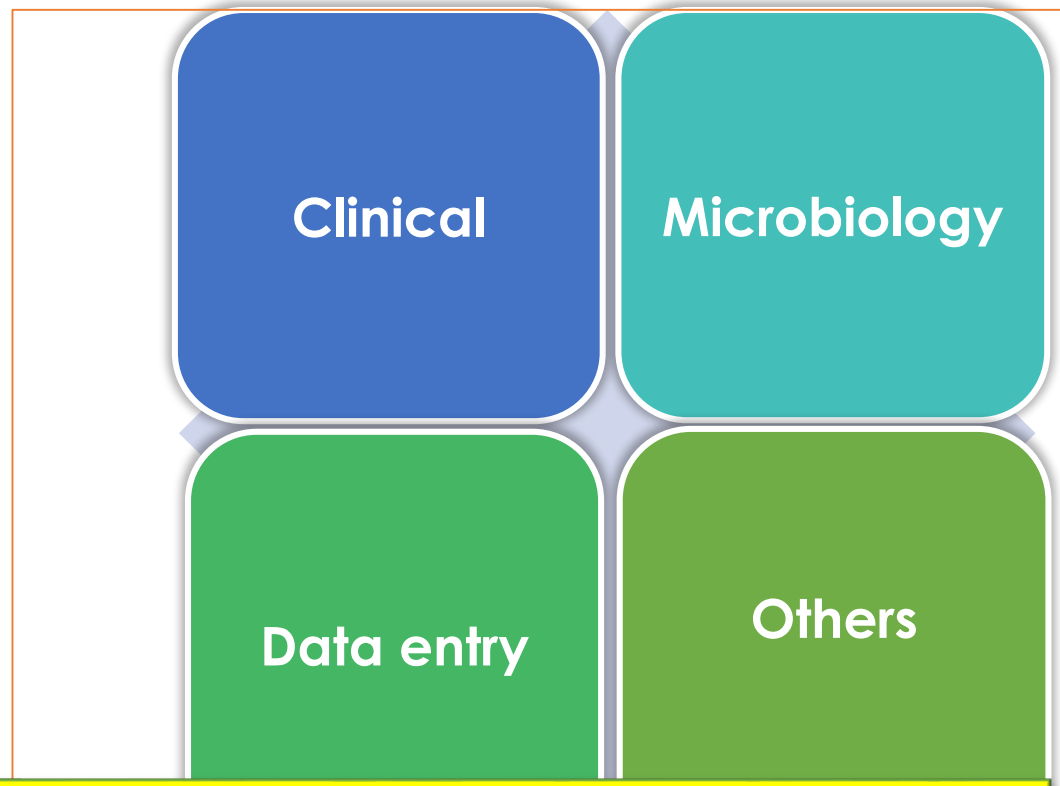
Uniform definitions

AJIC major articles

CDC/NHSN surveillance definition of health care–associated infection and criteria for specific types of infections in the acute care setting

Teresa C. Horan, MPH, Mary Andrus, RN, BA, CIC, and Margaret A. Dudeck, MPH
Atlanta, Georgia

Robust QC measures



Different from 'routine' data collection!

Methods

For all babies

PART B-1: ANTENATAL AND POSTNATAL DETAILS

Please encircle the following choices , unless otherwise specified

Details of the mother during antenatal period

No	Items	Response
25	Number of checkups/hospital visits during the antenatal period	
26	Parity	
27	Fever within 7 days before delivery	Y / N
28	UTI in last trimester	Y / N / NK
29	Any significant obstetric problem *Encircle more than one, if needed*	PIH / GDM / Anaemia / None
30	Antenatal steroids *(only if born preterm)*	Y / N / NK / NA
31	Any significant medical/surgical illness	Y / N
32	If yes, specify.....	
33	Received T.T.	Y / N

34	Received antibiotics	Before delivery		
		Antibiotic 1	Antibiotic 2	Antibiotic 3
	Code *			
	Duration of antibiotics (days)			

Details of the mother during labor/delivery

No	Items	Response
35	Number of vaginal examinations	
36	Duration of labor (in hrs)	h
37	Duration of rupture of membranes (in hrs)	h
38	Mode of delivery	Vaginal / Cesarean section / Forceps / Vacuum
39	Meconium stained liqor	Y / N / NK
40	Foul smelling liqor	Y / N / NK

41	Received antibiotics	After delivery		
		Antibiotic 1	Antibiotic 2	Antibiotic 3
	Code *			
	Duration of antibiotics (days)			

PART B-2: For extramural babies only

No	Items	Response
42	Cord cut by	New or sterile blade / Used or old blade / Scissors / Others
43	Cord tied by	Sterile clamp / Rubber band / Thread / Others
44	What was applied on the umbilical cord?	Nothing / Ghee / Antibiotic ointment or powder / Turmeric / Cow dung / Others (Specify)

PART D: DETAILS OF MONITORING

Instructions to fill *(*Fill the table below after collecting the information from the mother and/or from the patient file **once in 24 hrs** until discharge or death of the baby)

Please write 'Y' if yes or 'N' if no in the following boxes, unless otherwise specified

	Visit 1 ( )	Visit 2 ( )	Visit 3 ( )	Visit 4 ( )	Visit 5 ( )	Visit 6 ( )	Visit 7 ( )	Visit 8 ( )	Visit 9 ( )	Visit 10 ( )	Visit 11 ( )	Visit 12 ( )
Age (in hrs)												
Weight (in gms)												
Location of baby (1= NICU,2=Post natal ward,3=Emergency,4= Intermediate care unit)												
Is mother involved in baby care												
KMC (Kangaroo mother care in completed hrs)												
Total fluid intake in the last 24 hrs												
IV fluids ***(ml)***												
Formula/Top milk ***(ml)***												
Expressed breast milk ***(ml)***												
If breastfed, number of breastfeeding sessions												
Skin breach												
Intra gastric tube												
Peripheral IV cannula												
Thrombophlebitis /Extravasation												
Parenteral nutrition												
PICC line												
Umbilical venous catheter												
Umbilical arterial catheter												
Umbilical infection												
Peripheral arterial line												
RBCs/Plasma/Platelet transfusion since last visit												
Exchange transfusion since last visit												
Free-flow oxygen												
CPAP												
IMV												
Urinary catheter												
MEDICATIONS & INFUSIONS												
Maximum no of infusions (>1hr)												

Prospective daily collection of risk factors!

(more than 50 variables; nearly 100 visits)

Results

THE LANCET Global Health

Characterisation and antimicrobial resistance of sepsis pathogens in neonates born in tertiary care centres in Delhi, India: a cohort study

*Investigators of the Delhi Neonatal Infection Study (DeNIS) collaboration**

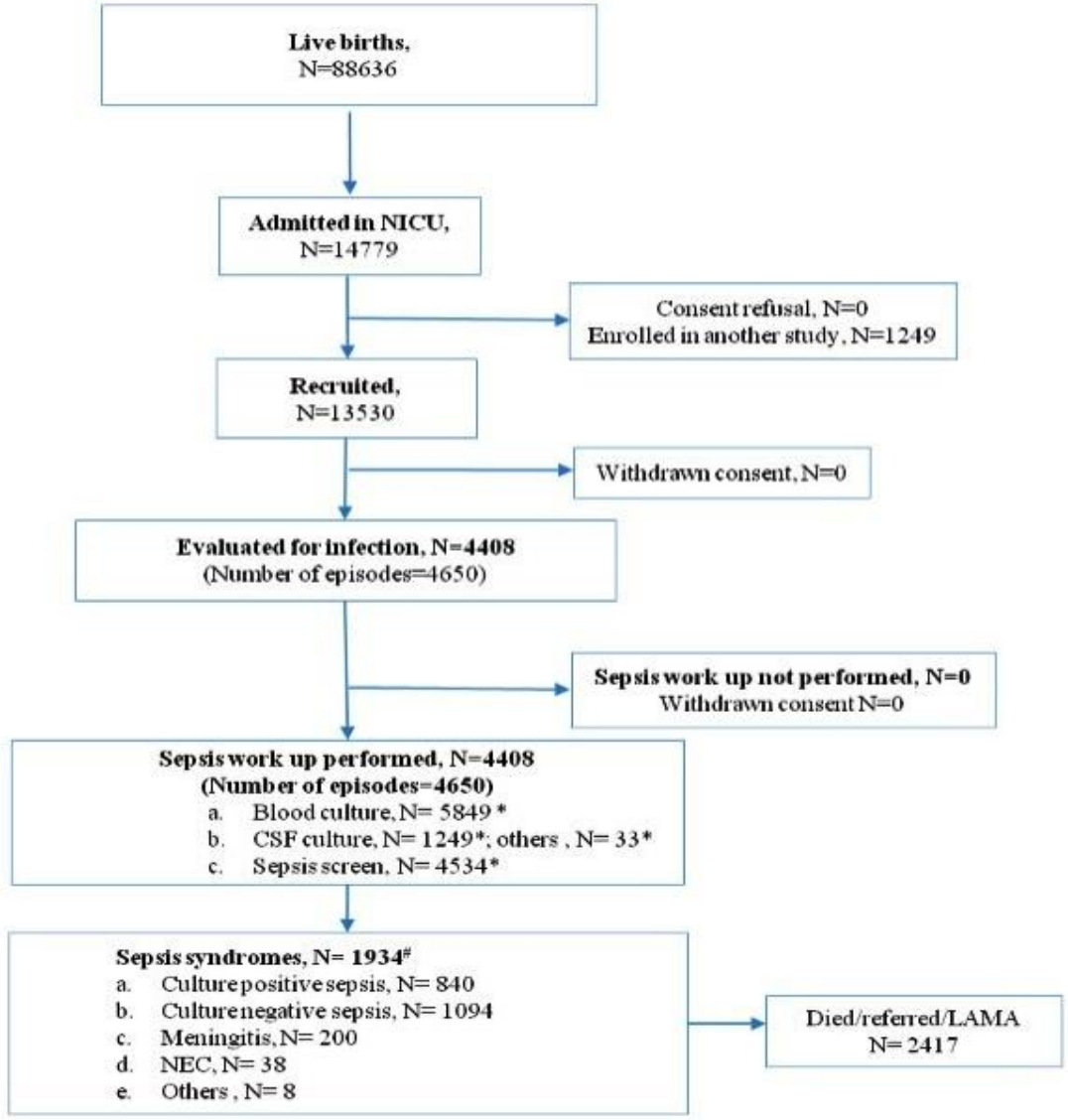
PLOS ONE

RESEARCH ARTICLE

Alarming rates of antimicrobial resistance and fungal sepsis in outborn neonates in North India

Study flow

July 2011 to February 2014



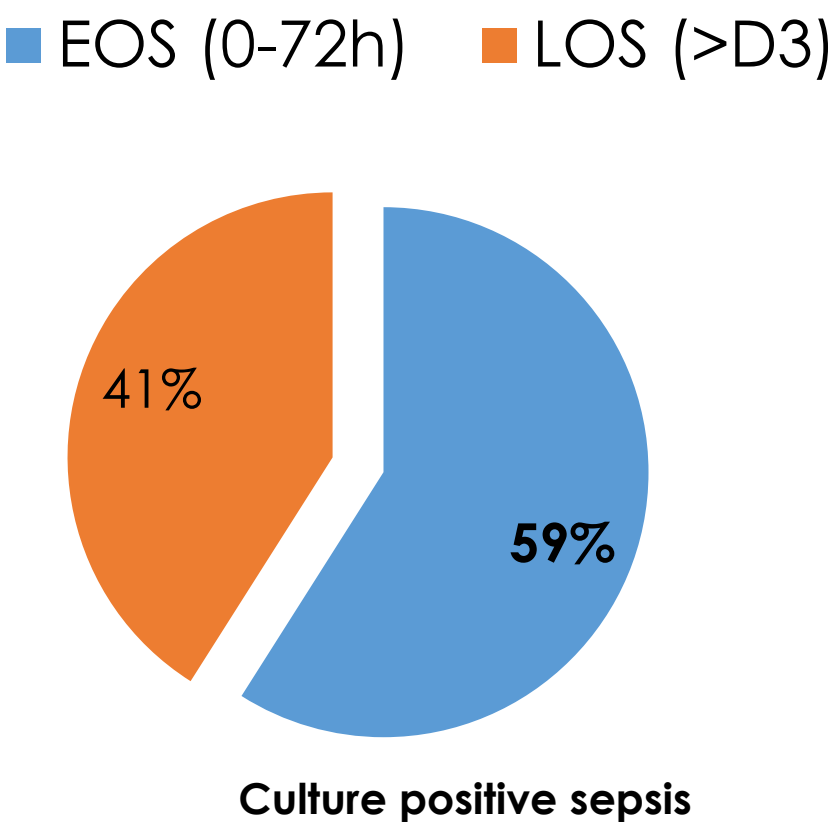
Results

N= 13530

	Total sepsis	Culture positive sepsis
Incidence	14.3%	6.2%
CFR	25.6%	47.6%

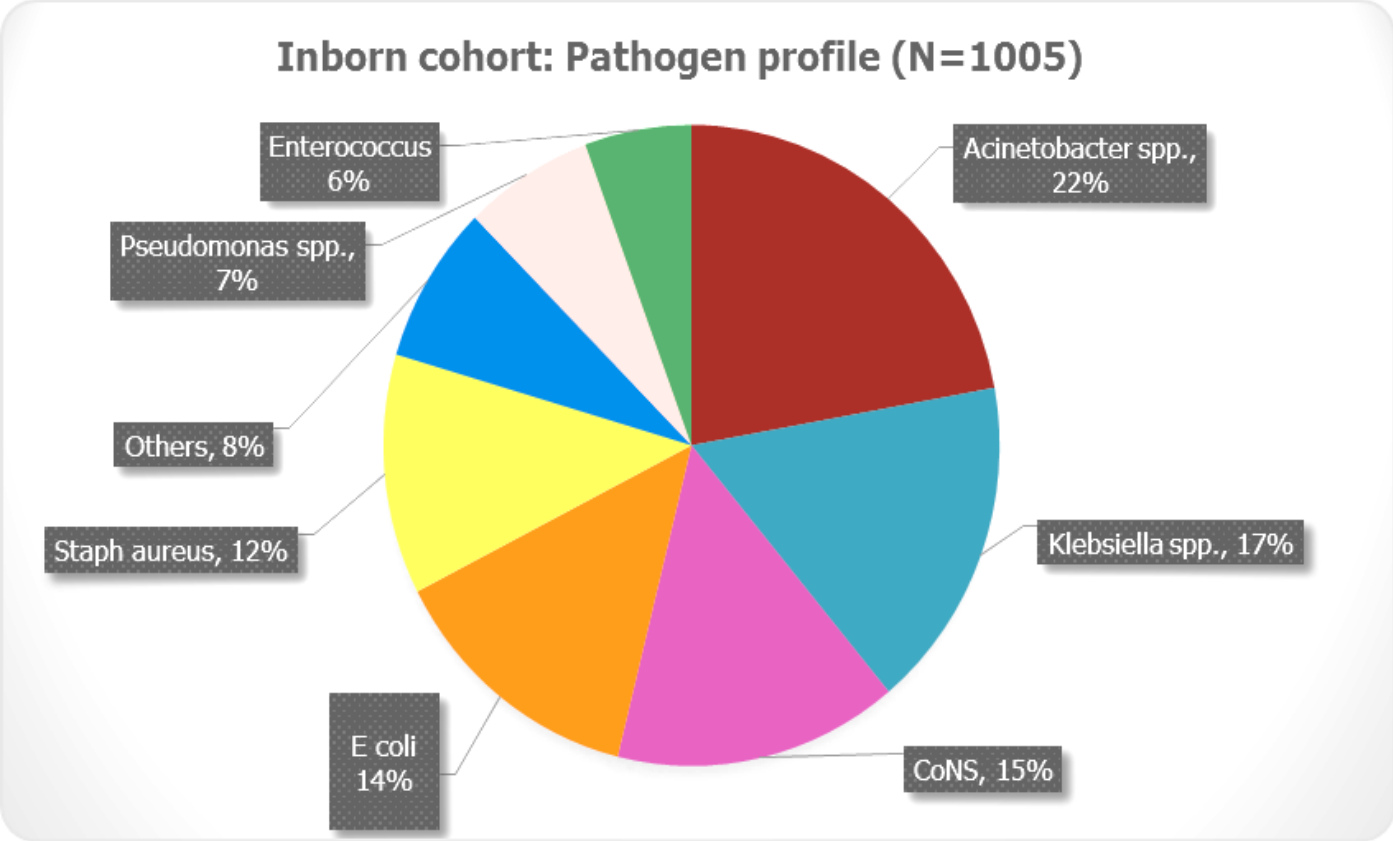
High burden of sepsis & high CFR

Onset



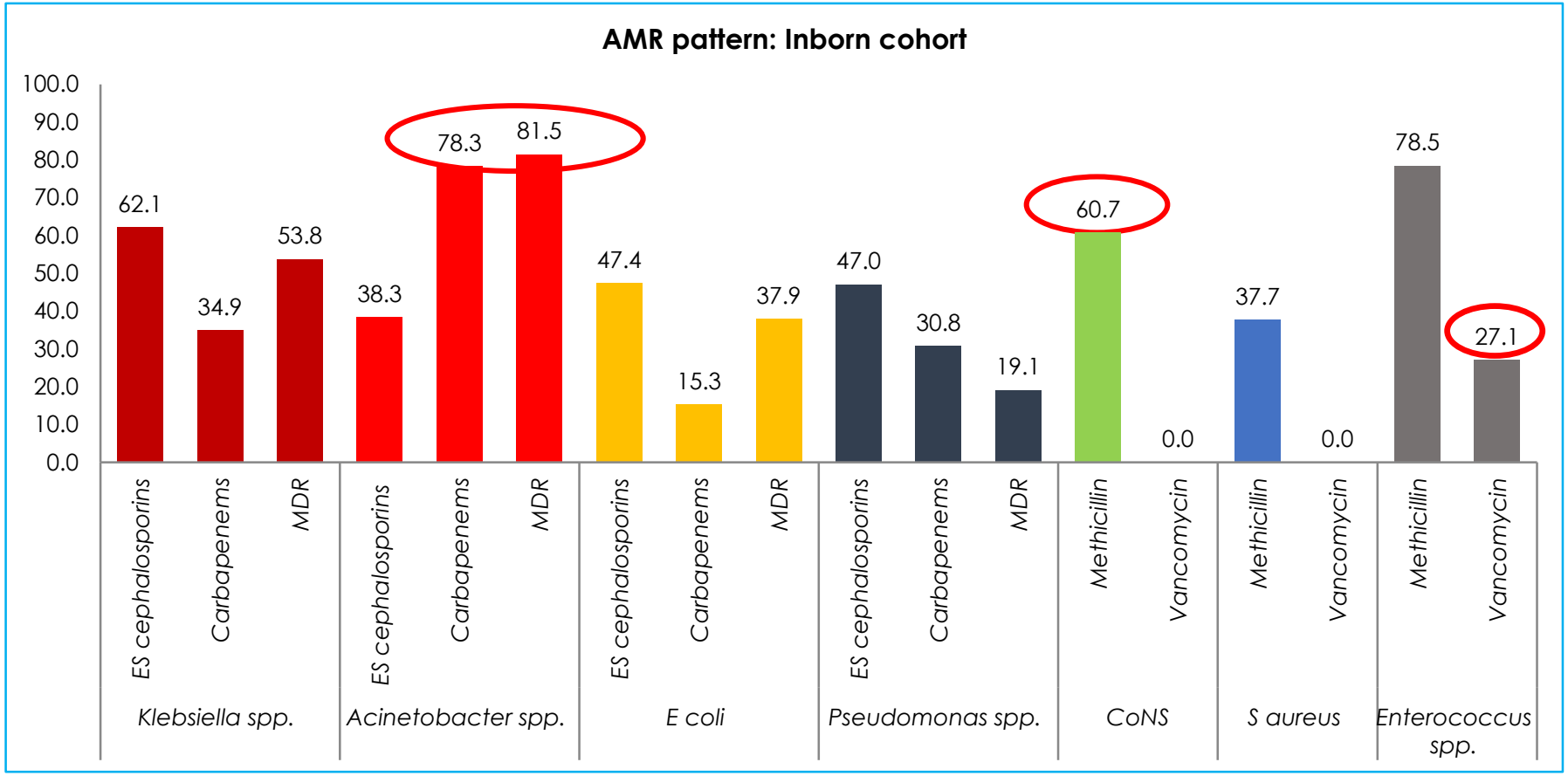
Most sepsis occurs early

Pathogen profile

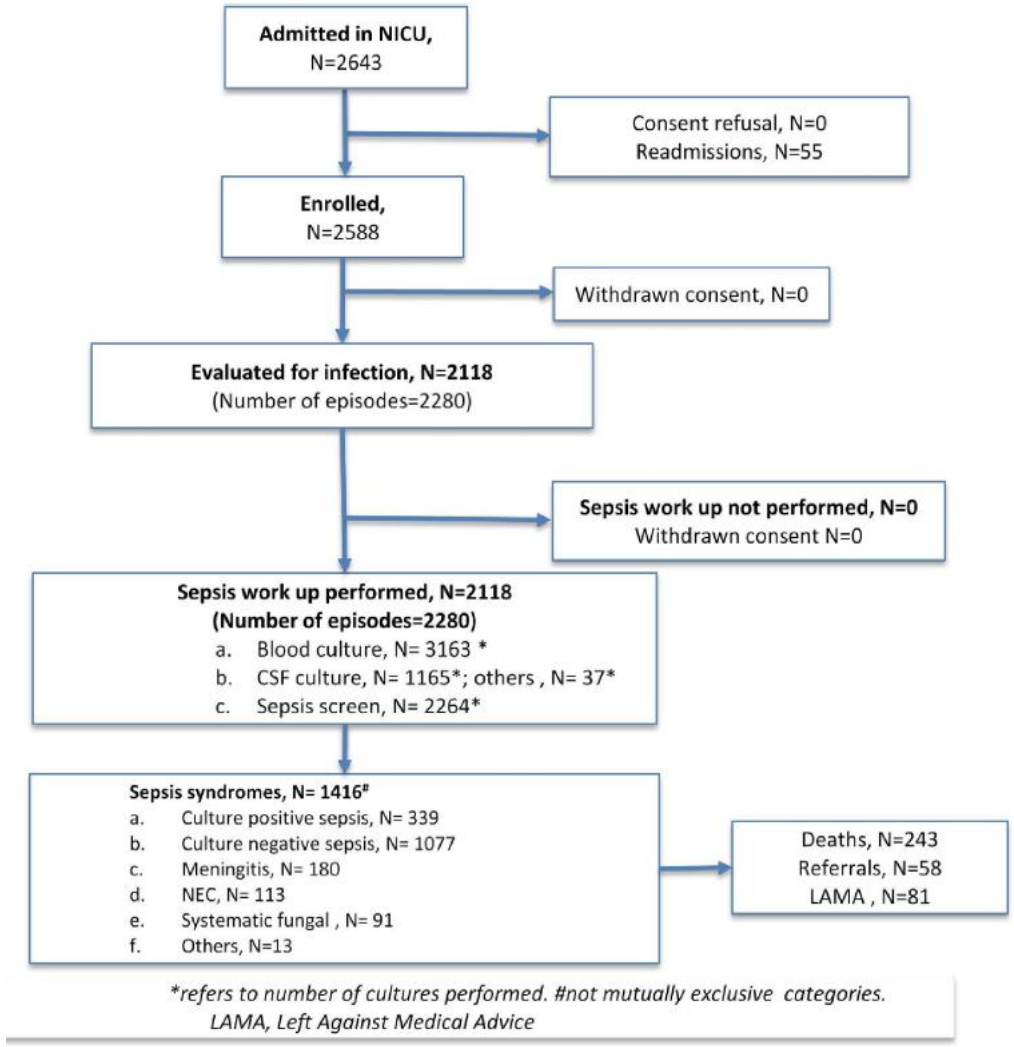


Acinetobacter: the new 'King'!

Antimicrobial resistance (AMR)



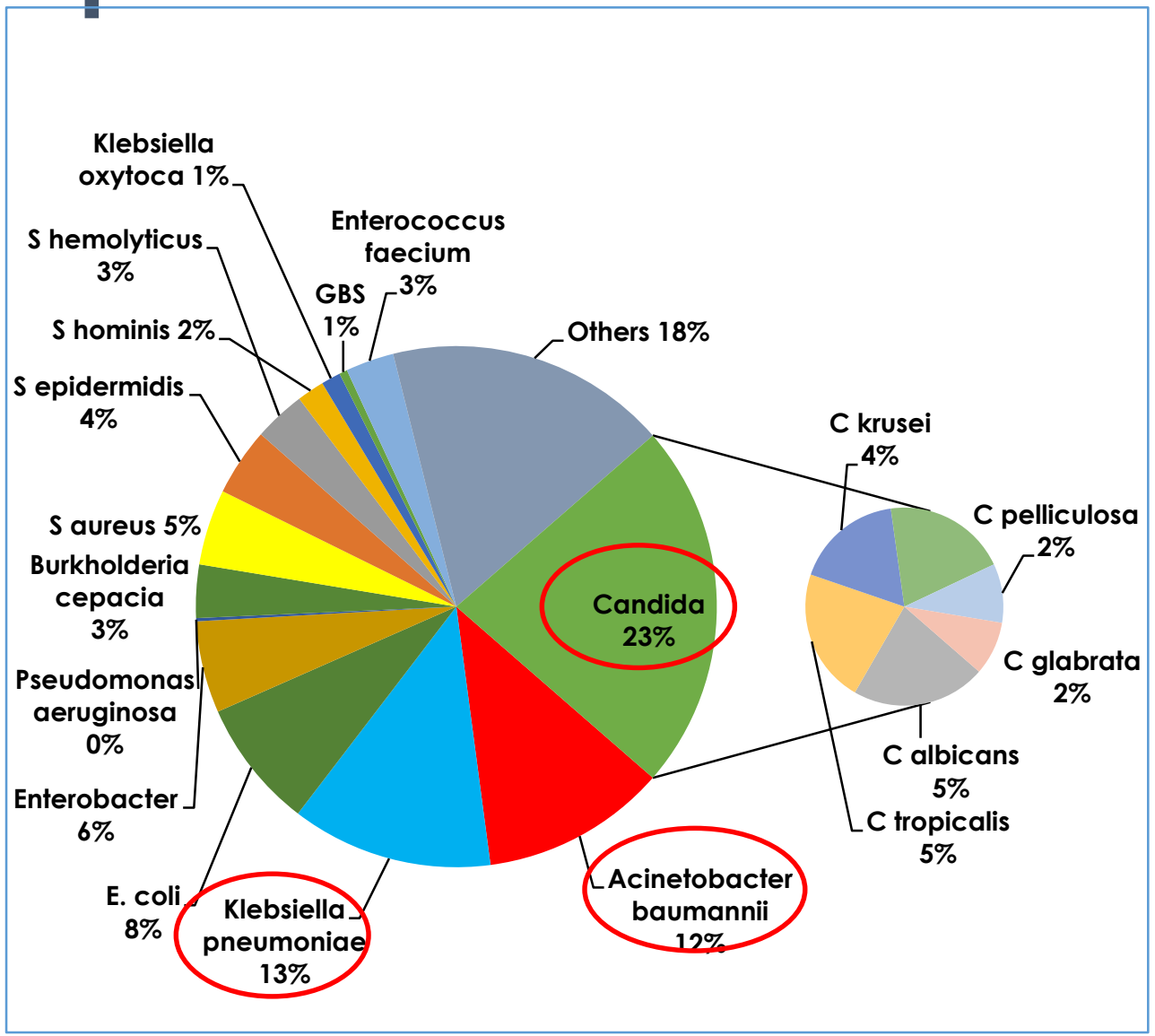
Outborn cohort



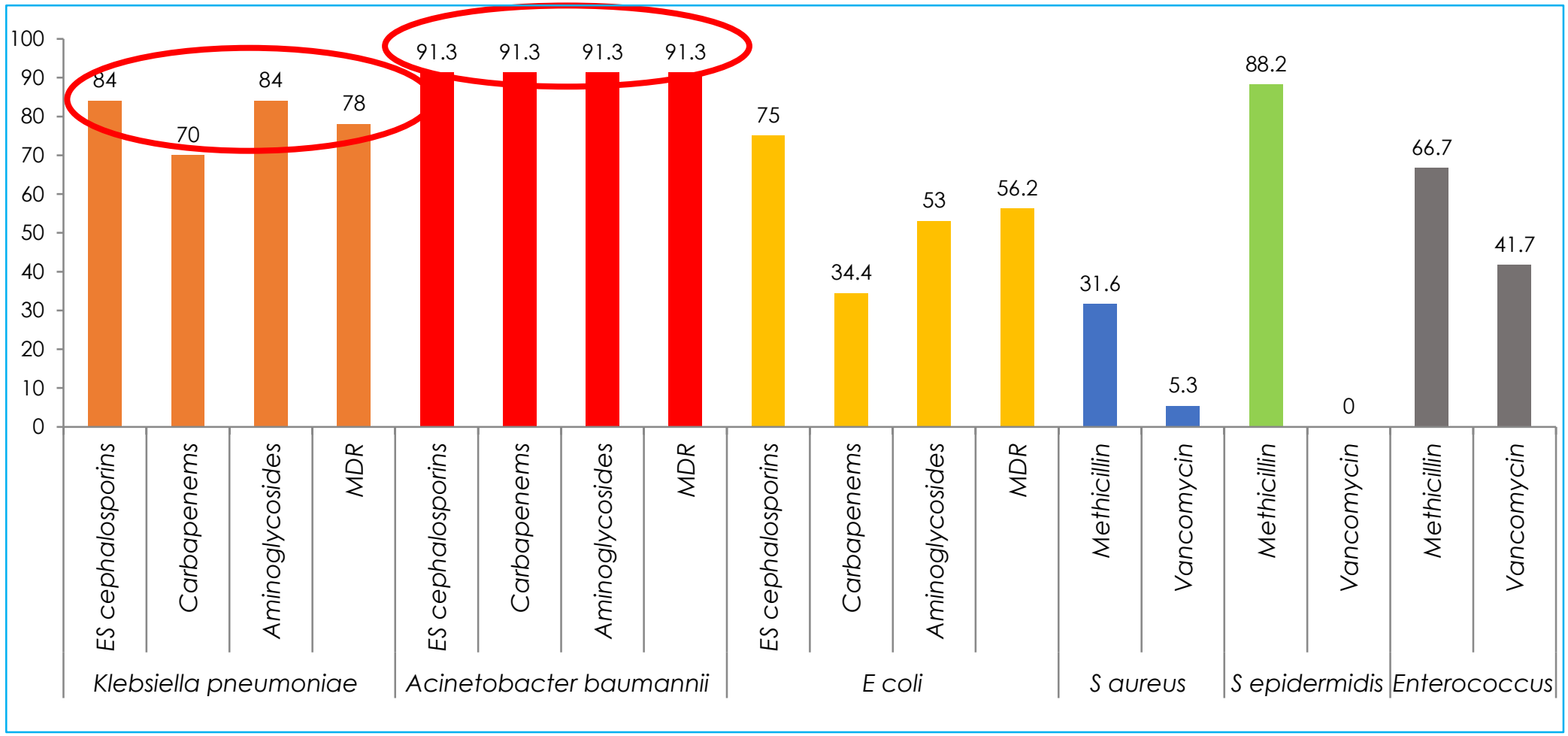
Results

Characteristics	Values (n = 2588)
Birth weight, g (n= 2058)	**2204±731**
Gestation, weeks (n=2583)	**35.4±2.8**
Male gender	1680 (64.9%)
Age at admission, days	5 (2-11)
Maternal fever within 7 days prior to delivery	211/2303 (9.2%)
Foul smelling liquor	53/2550 (2.1%)
Home delivery	**550/2588 (21.2%)**
Did not cry at birth	**643/2577 (24.9%)**
Unhygienic cord practices	**879/2544 (34.5%)**
Previous hospitalization	**984 (38.0%)**
Primary/secondary level government hospital	56 (5.7%)
Tertiary level government hospital	198 (20.1%)
Private hospital	730 (74.2%)
Previous antibiotic therapy	**825/984 (83.4%)**

Pathogen profile



Antimicrobial resistance



Quality issues & solutions

Issues: Clinical

- Assigning ‘label’ of sepsis
- Sample collection
  - Contaminants
- Routine surveillance cultures

Issues: Microbiology

- Contaminants
  - Definition
  - Growth in cultures
- Varied isolation rates
- Automated vs. manual cultures
- Antibiotics used for AST

Issues & solutions: Clinical

1. Assigning the label of sepsis

Problem	Solutions identified
Baby receiving antibiotics for 5-7 days, but final diagnosis "no septicemia"	1. **PIs' meeting** to develop **consensus** 2. Assigning the **diagnosis by PI/co-PI** in a **prospective** manner 3. Use standard definitions – **CDC/NHSN criteria**

Using CDC Definitions
(modified after extensive discussions with site PIs)

Issues & solutions: Clinical

2. Sample collection

Problem	Solutions identified
Growth of skin contaminants	1. **Training of nurses** – proper skin preparation, using aseptic precautions 2. **Video** for demonstration – weekly reinforcement 3. **Site visits by the SRO/Scientist** 4. Gradually shift the responsibility of blood collection to nurses at all sites

Training and supervision!

Issues & solutions: Clinical

3. Routine surveillance cultures

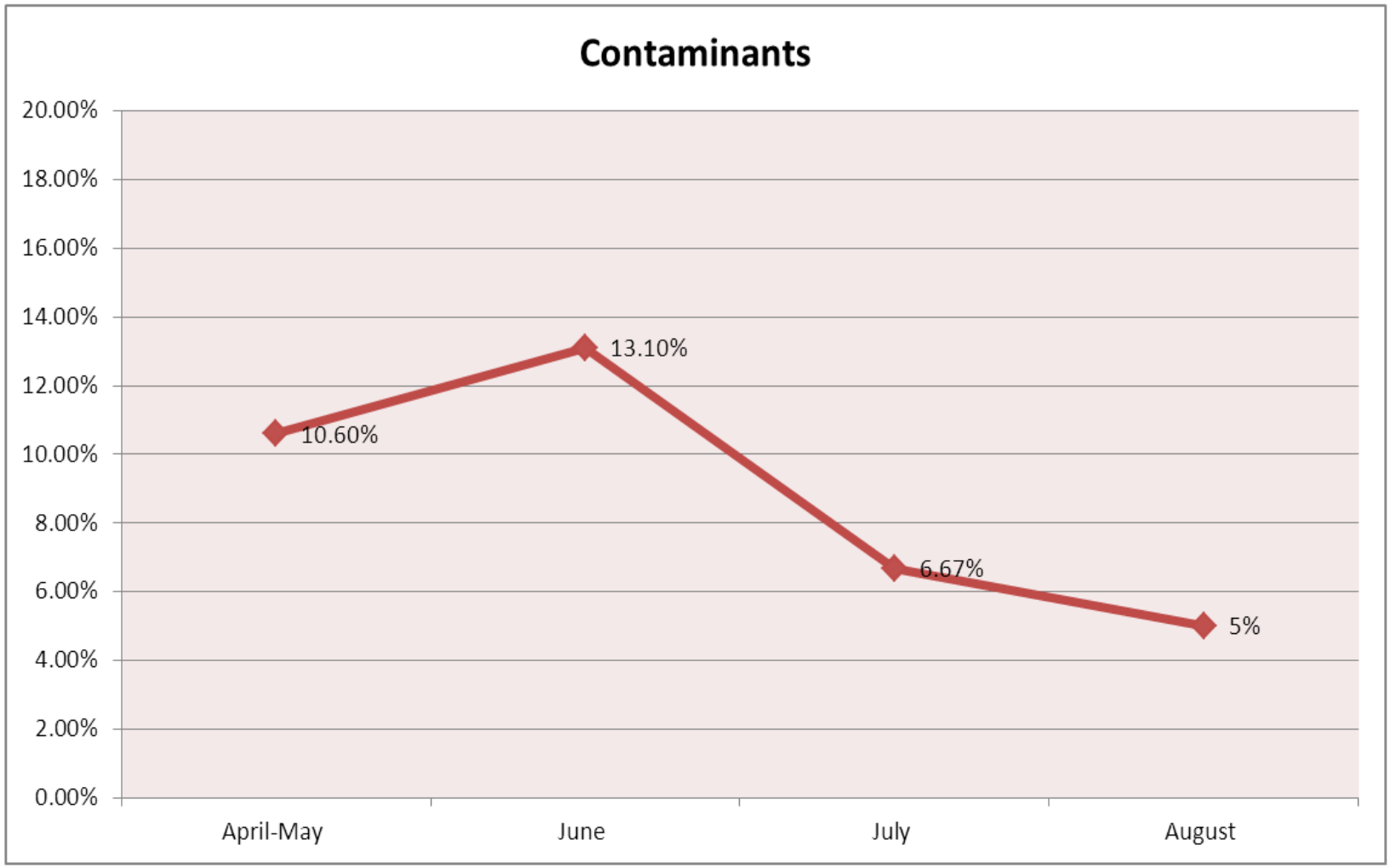
Problem	Solutions identified
Cultures sent after intubation, exchange transfusion, PICC line removal, etc.	1. **PIs' meeting:** decision to disregard these cultures for the study purpose 2. Ensure strict **compliance to SOP**

Consensus meetings!

Issues & solutions: Microbiology

1. Contaminants

Problem	Solutions identified
1. Media prepared by routine staff 2. Problems in autoclaving, etc.	• **Media** to be prepared **by research staff** • Date of autoclaving to be affixed • **'Sterility check'** – one bottle from each batch to be incubated overnight • **Unused** media to be **returned** within 5-7 days • Nurses to check if media is clear before inoculation


Contaminants
20.00%
18.00%
16.00%
14.00%
12.00%
10.00%
8.00%
6.00%
4.00%
2.00%
0.00%
10.60%
13.10%
6.67%
5%
April-May
June
July
August

Issues & solutions: Microbiology

2. Definition of contaminants

Problem	Solutions identified
1. **No consistent definition** across study sites	1.PIs' meeting – **consensus**: • ASB and diphtheroids • Growth of 3 or more organisms • CoNS from CSF

Issues & solutions: Microbiology

3. Varied isolatio

Probl	identified
1. Low isolatio some study s 2.Isolation of c from CSF - lo	**neck** for ability to rial growth ro store samples culation of CSF in es

Issues & solutions: Microbiology

4. Use of automated system for identification

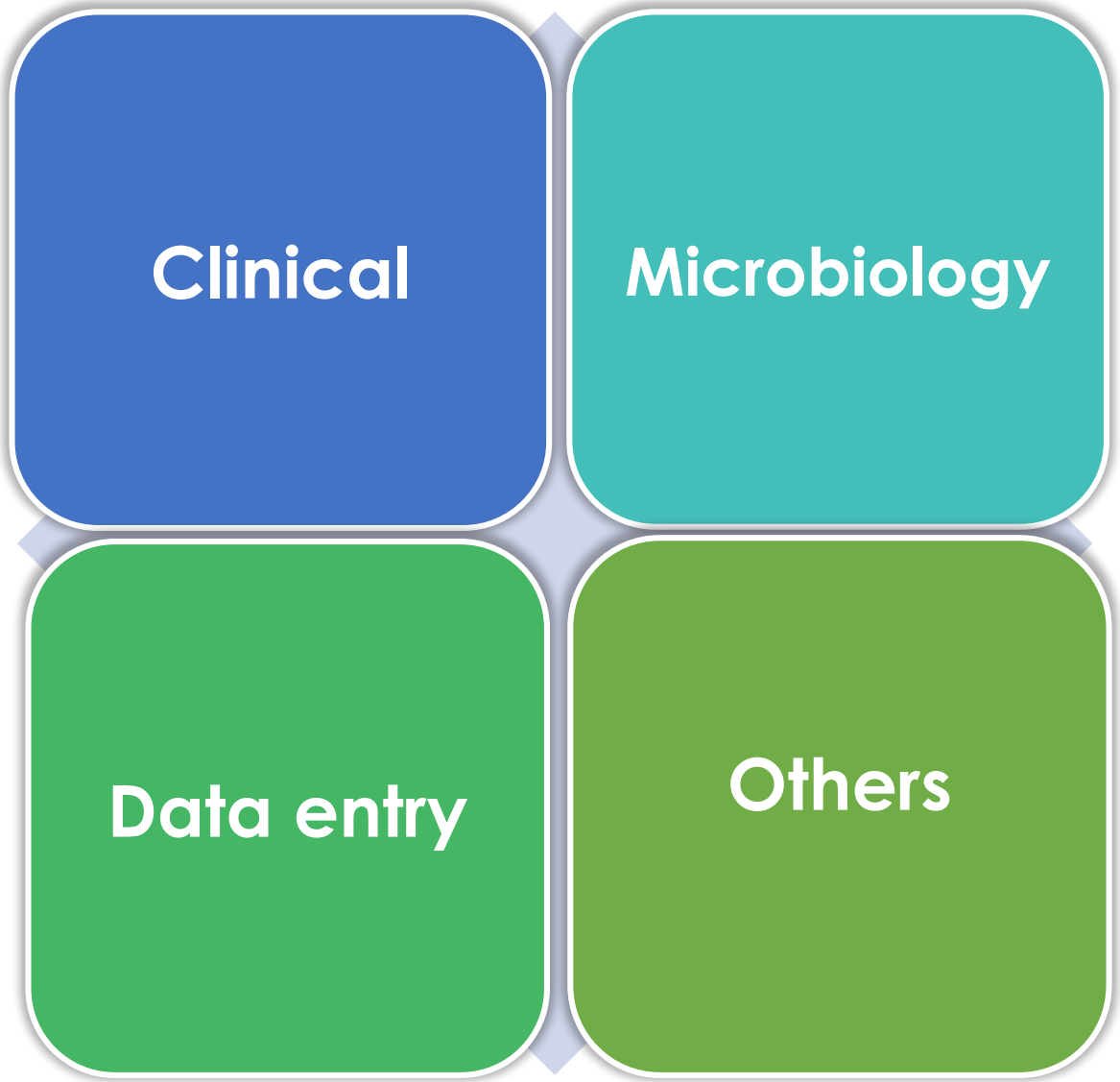
Problem	Solutions identified
1.Some centers use Vitek cards while others use conventional techniques 2.Unusual organisms being reported from Vitek	• Try automated technique in all; • Unusual organisms – final reporting after manual check • EQAS

Issues & solutions: Microbiology

5. Antibiotics for AST

Problem	Solutions identified
1. Antibiotics used at each study site were different 2.Different cut-offs used for definition of resistance	• Consensus - choice of antibiotics to be used • CLSI or European Standard guidelines to be used for determining the cut-offs

Quality assurance (QA)

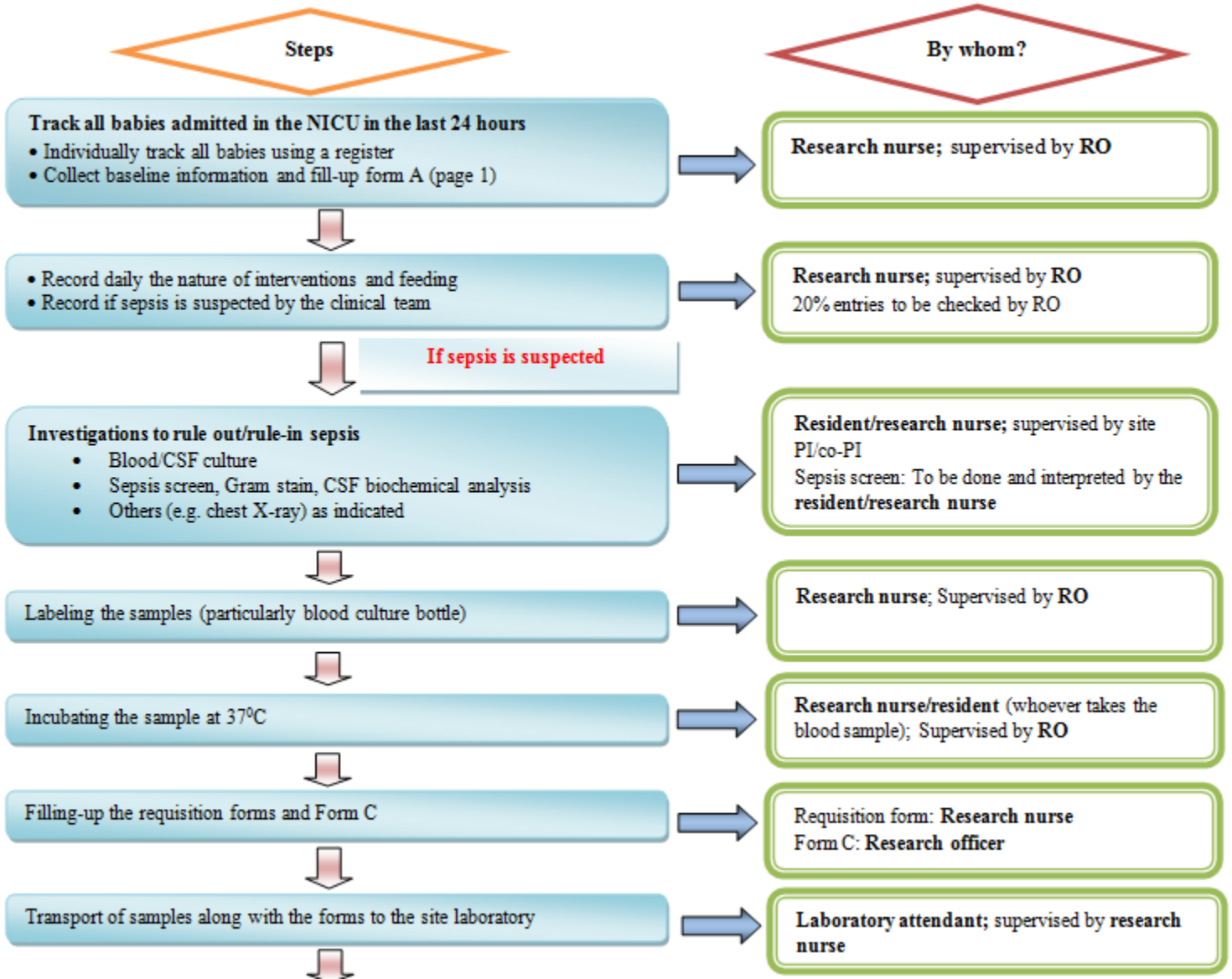

Clinical
Microbiology
Data entry
Others

Tools

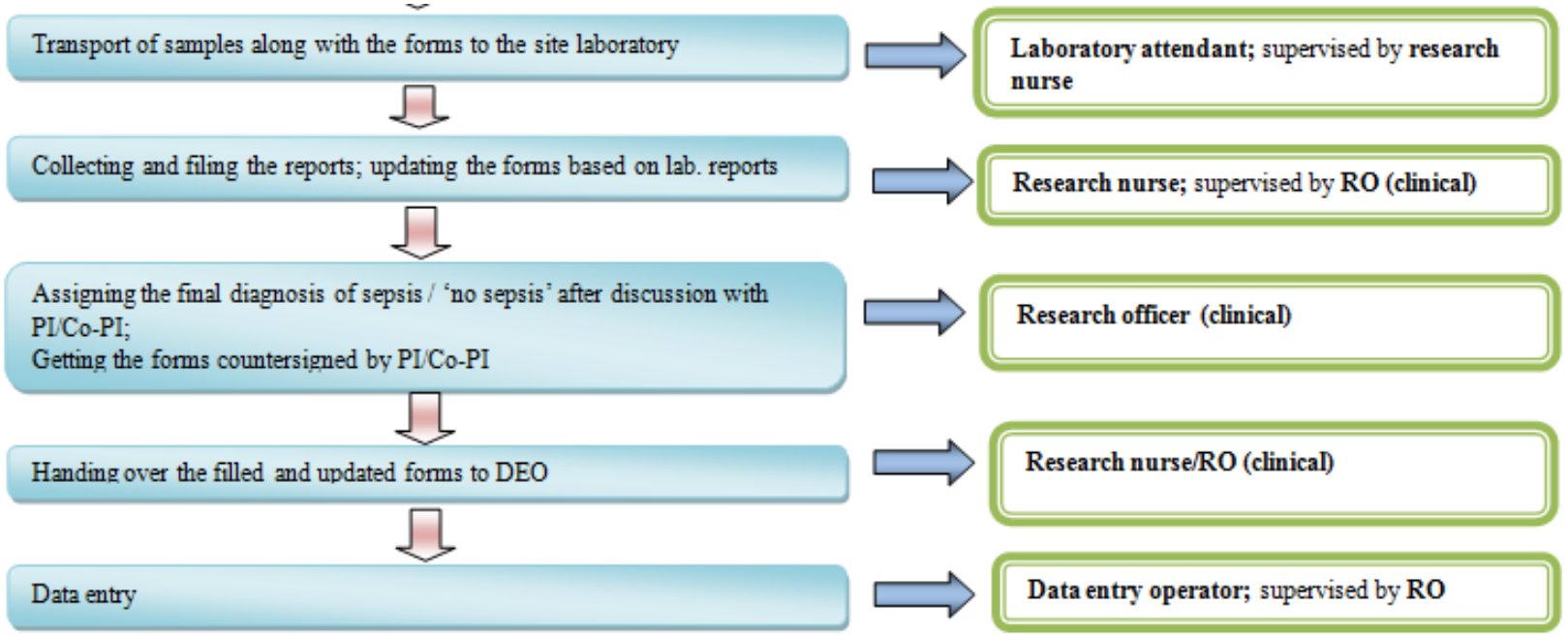
- **Standard operating procedures (SOP)**
- **SOPs for filling forms A & C**
- Data entry interface
  - Training manual
- Videos

Quiz to ensure strict adherence to SOP!

SOP


Steps
By whom?
Track all babies admitted in the NICU in the last 24 hours
• Individually track all babies using a register
• Collect baseline information and fill-up form A (page 1)
Research nurse; supervised by RO
• Record daily the nature of interventions and feeding
• Record if sepsis is suspected by the clinical team
Research nurse; supervised by RO
20% entries to be checked by RO
If sepsis is suspected
Investigations to rule out/rule-in sepsis
• Blood/CSF culture
• Sepsis screen, Gram stain, CSF biochemical analysis
• Others (e.g. chest X-ray) as indicated
Resident/research nurse; supervised by site PI/co-PI
Sepsis screen: To be done and interpreted by the resident/research nurse
Labeling the samples (particularly blood culture bottle)
Research nurse; Supervised by RO
Incubating the sample at 37°C
Research nurse/resident (whoever takes the blood sample); Supervised by RO
Filling-up the requisition forms and Form C
Requisition form: Research nurse
Form C: Research officer
Transport of samples along with the forms to the site laboratory
Laboratory attendant; supervised by research nurse

SOP


Transport of samples along with the forms to the site laboratory
Laboratory attendant; supervised by research nurse
Collecting and filing the reports; updating the forms based on lab. reports
Research nurse; supervised by RO (clinical)
Assigning the final diagnosis of sepsis / 'no sepsis' after discussion with PI/Co-PI;
Getting the forms countersigned by PI/Co-PI
Research officer (clinical)
Handing over the filled and updated forms to DEO
Research nurse/RO (clinical)
Data entry
Data entry operator; supervised by RO

QA: Clinical

Steps

- Nodal team visits
- Fortnightly review meetings
- PI meeting

QA: Clinical

Nodal team visits

- Weekly visit by co-PI/SRO to all the sites
- Monitoring of enrolment, data collection and recording
- Cross checking CRFs
  - 10% CRFs randomly cross-checked
  - Errors noted & communicated to site PI/co-PI
- Reviewing technique of blood/CSF cultures by research staff

QA: Clinical

Fortnightly review meetings

- To summarize ongoing activities at each site
  - Data from each site is presented
- Attended by ROs from all sites
- Issues at any site discussed and feedback provided

QA: Clinical

PI meetings

- To update the progress made
- To discuss and resolve contentious issues
- Pivotal to resolve major issues like definition of clinical sepsis, panel of antibiotics to be tested for AST

QA: Microbiology

- Internal quality control
- External quality control
- Viability check of glycerol stocks

Internal quality control

Media sterility

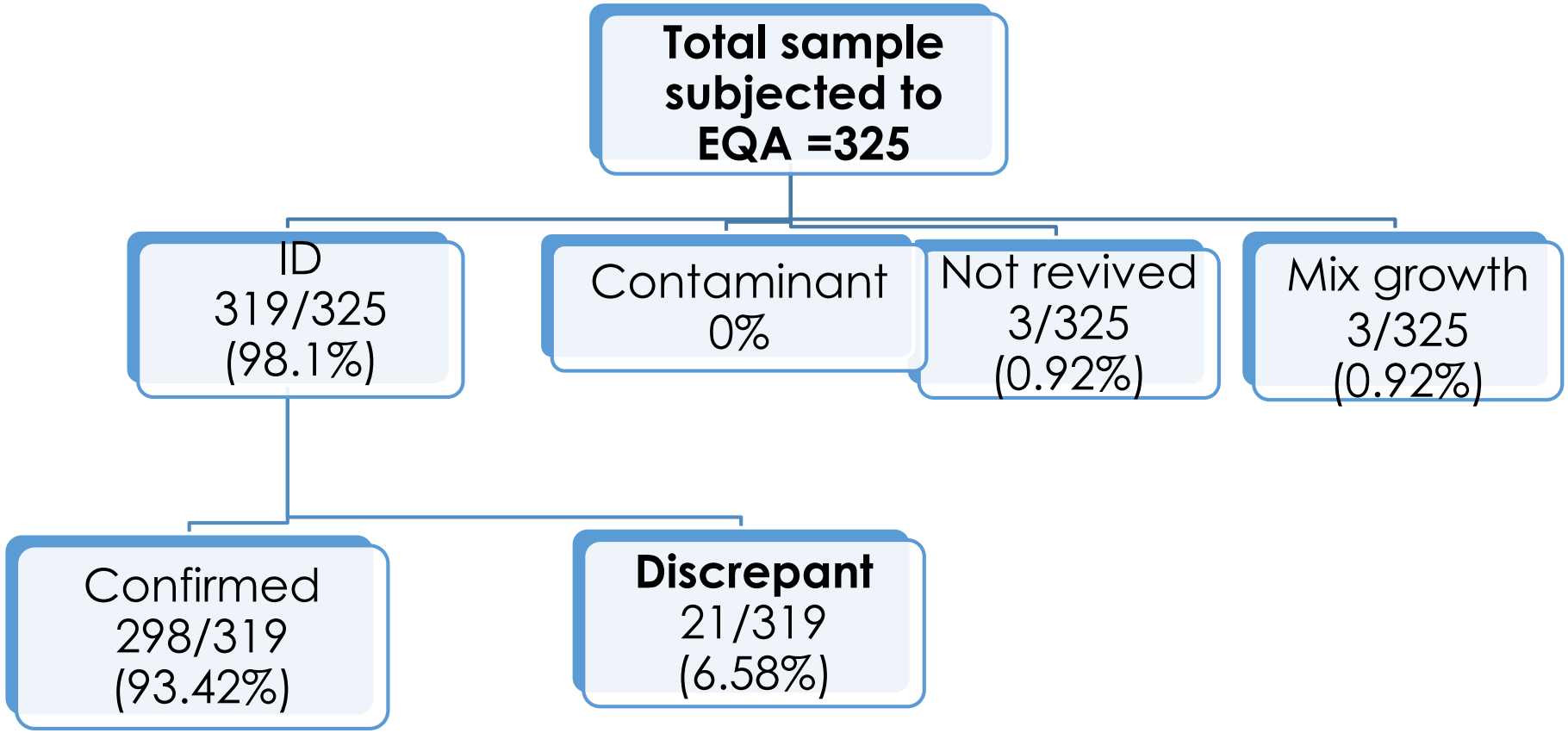
- Sterility checked by incubating sterile culture plate at 37^0C overnight
- No growth = 'sterile'

Ability to support the growth

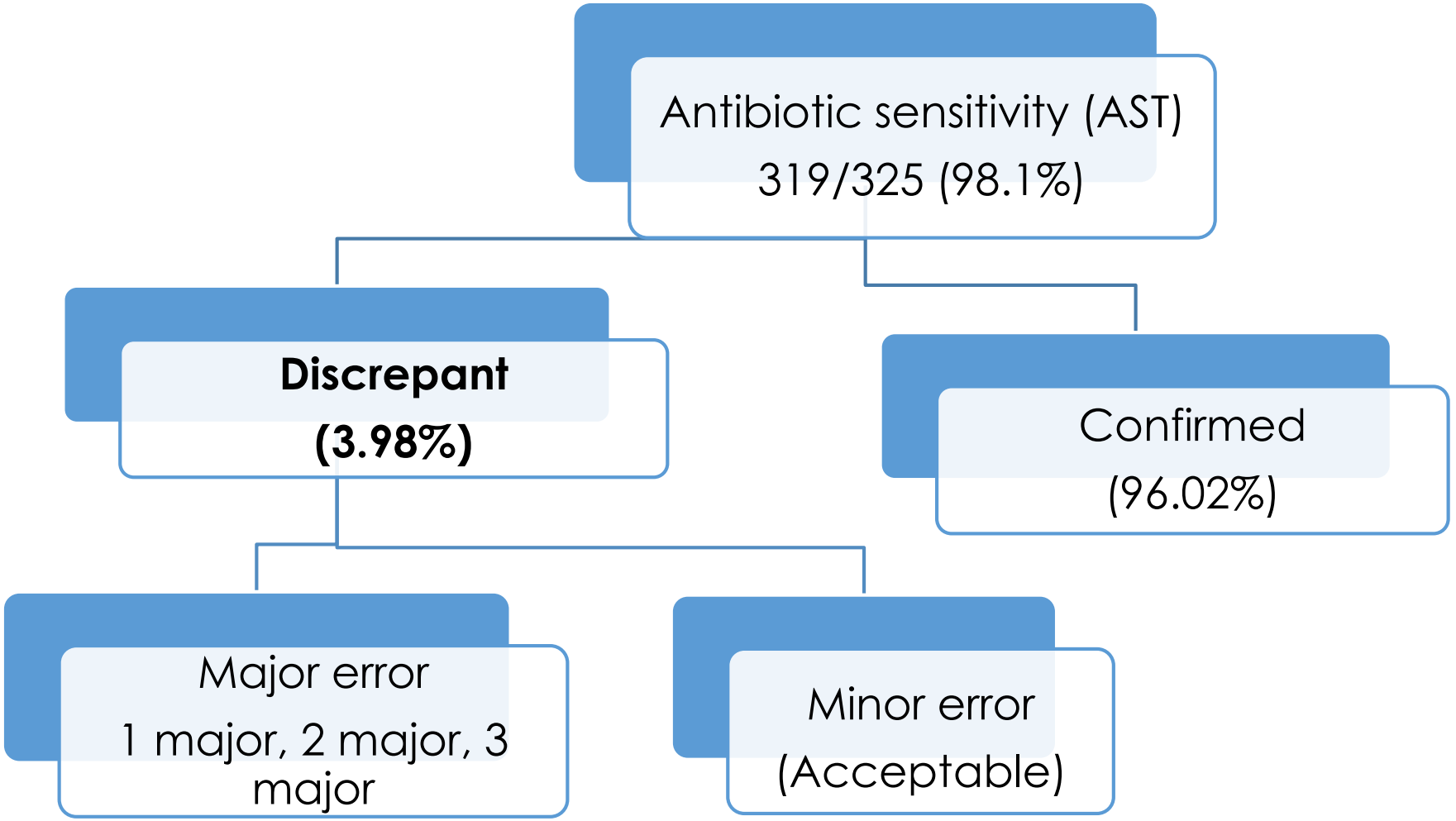
- Sterile media on culturing with control strain should grow after overnight incubation at 37^0C

External quality assessment (EQA)

- Done twice a year
- Initially ~45% isolates taken for EQA
- 10% of samples from each site
- Samples picked randomly



Overall concordance:93.4%



Overall concordance: 96.0%

Viability of glycerol stocks

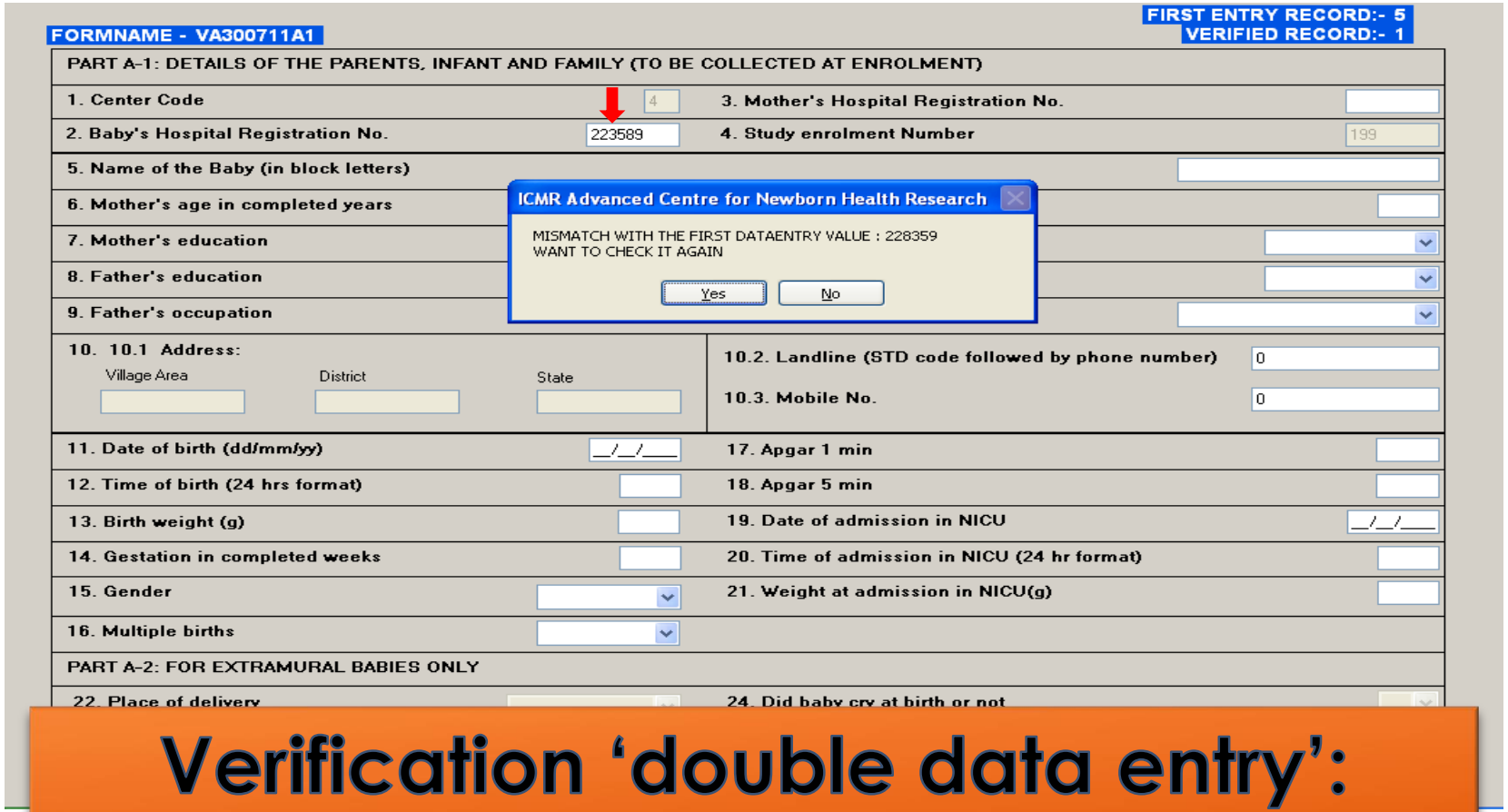
- All glycerol stocks checked for viability q6 months by the reference lab
- Once revived, the fresh stocks were generated, labeled and stored with the new date

QA: Data entry

Done by

1. Double data entry
2. Site visits
3. Logical checks

Double data entry



Verification 'double data entry': interactive mode

Mismatch report

	A	B	C	D	E	F	G	H	I	J
1	BATCH_NAME	CCODE	ENRLNO	FIELD_NAME	OLD_VALUE	NEW_VALUE	FDE_NAME	DT_CHANGE	ERROR_TYPE	VDE_NAME
2	090212A1	4	457	CULREPORT1		TRUE	VIKAS	21/02/2012 12:11	MISMATCH DATA ENTRY	PRATIBHA
3	090212A1	4	457	FINALDIAG1		Y	VIKAS	21/02/2012 12:11	MISMATCH DATA ENTRY	PRATIBHA
4	090212A1	4	457	SEPNO1ANTI1	0	6	VIKAS	21/02/2012 12:11	MISMATCH DATA ENTRY	PRATIBHA
5	090212A1	4	457	SEPNO1ANTI2	0	13	VIKAS	21/02/2012 12:11	MISMATCH DATA ENTRY	PRATIBHA
6	090212A1	4	457	SEPNO1ANTI3	0	22	VIKAS	21/02/2012 12:11	MISMATCH DATA ENTRY	PRATIBHA
7	090212A1	4	457	SEPNO1DUR1	0	13	VIKAS	21/02/2012 12:12	MISMATCH DATA ENTRY	PRATIBHA
8	090212A1	4	457	SEPNO1DUR2	0	15	VIKAS	21/02/2012 12:12	MISMATCH DATA ENTRY	PRATIBHA
9	090212A1	4	457	SEPNO1DUR3	0	10	VIKAS	21/02/2012 12:12	MISMATCH DATA ENTRY	PRATIBHA
10	090212A1	4	576	DISTRICT	TIRLOK PURI	TRILOK PURI	VIKAS	21/02/2012 15:15	MISMATCH DATA ENTRY	PRATIBHA
11	090212A1	4	576	NOCHECKUP	9	4	VIKAS	21/02/2012 15:17	MISMATCH DATA ENTRY	PRATIBHA
12	120312M1	2	1052	COD_PREMATU		N	MANISH	16/03/2012 10:55	MISMATCH DATA ENTRY	AANCHAL
13	080312C1	1	608	COD_PREMATU		N	AANCHAL	20/03/2012 11:26	MISMATCH DATA ENTRY	MANISH
14	220312S1	3	3678	PRIORFEED	NOT APPLICABLE	EXCLUSIVELY BREAST MILK	SHIL	29/03/2012 14:56	MISMATCH DATA ENTRY	NISHA
15	220312S1	3	3689	BNAME	NANGEETA	SANGEETA	SHIL	29/03/2012 15:51	MISMATCH DATA ENTRY	NISHA
16	220312S1	3	3716	BNAME	PUSPA	PUSHPA 2	SHIL	31/03/2012 10:56	MISMATCH DATA ENTRY	NISHA
17	220312S1	3	3716	UTI	N		SHIL	31/03/2012 10:58	MISMATCH DATA ENTRY	NISHA
18	220312S1	3	3716	CULREPORT1		STERILE	SHIL	31/03/2012 11:00	MISMATCH DATA ENTRY	NISHA
19	220312S1	3	3716	FINALDIAG1		N	SHIL	31/03/2012 11:00	MISMATCH DATA ENTRY	NISHA
20	220312S1	3	3716	SEPNO1ANTI1	0	1	SHIL	31/03/2012 11:00	MISMATCH DATA ENTRY	NISHA
21	220312S1	3	3716	SEPNO1ANTI2	0	22	SHIL	31/03/2012 11:00	MISMATCH DATA ENTRY	NISHA
22	220312S1	3	3716	SEPNO1ANTI3	0	18	SHIL	31/03/2012 11:00	MISMATCH DATA ENTRY	NISHA

QA: Data entry

Visits by nodal team

- 10% forms randomly selected from each batch
- Cross checked with entered data
- Calculate error rate
  - ✓If >10%, whole batch is rejected; DEO will re-enter data
  - ✓If <10%, errors are corrected

Site visits

Site Visit Report

Date: 26-11-2011

Visiting Team member
Mr. S.S. Suresh

Participating Centre (SJH)
Ms. Nisha (SJH)

The coordinating center team made the second visit on 25/11/11 at the SJH for data accuracy checks.

Following Batches have been selected; at random10% forms have been checked for each batch. Minor mistakes have been found which are under the tolerable limit.

Details of sampling are given below:

Centre Name	Form Name	Batch Name	Total No. forms in the Batch	No. of forms Checked	Enrollment Number of checked forms	Remarks
SJH	Form A	160811S1	20	2	1283,1316	Satisfactory
		170811S1	10	2	1329,1342	Satisfactory
		180811S1	20	2	1360,1377	Satisfactory
		190811S1	20	2	1388,1406	Satisfactory
		200811S1	20	2	1239,1415	Satisfactory
		230811S1	20	2	1422,1428	Satisfactory
		150911S1	34	3	1740,1810,1843	Satisfactory
SJH	Form C	150911S1	40	4	1745,1770,1811,1813	Satisfactory
		190911S1	34	3	1791,1818,1860	Satisfactory

Site visits

Some Errors have been detected during visit which are recorded and corrected in the data base.

Error in FORM A				
Centre Name	**Enrollment Number**	**Variable Name**	**Filled Value**	**Entered Value**
SJH	1239	BHRN	64377	643747

Errors in Form A Visit Entry					
Centre Name	**Enrollment Number**	**Visit No.**	**Variable Name**	**Filled Value**	**Entered Value**
SJH	1329	1	REPEATCUL	N	Y
	1843	3	AGEHRS	92	42
	1283	2	IVFLUID	114	14

Errors in FORM C				
Centre Name	**Enrollment Number**	**Variable Name**	**Filled Value**	**Entered Value**
SJH	1811	SEPSCREEN	NEGATIVE	NOT DONE

The visiting team is thankful to the DEO of SJH center for their cooperation and support during the visit.

QA: Data entry

Logical checks

- ‘form filling errors’ and
- ‘data entry errors’ not corrected by double data entry

List of logical checks

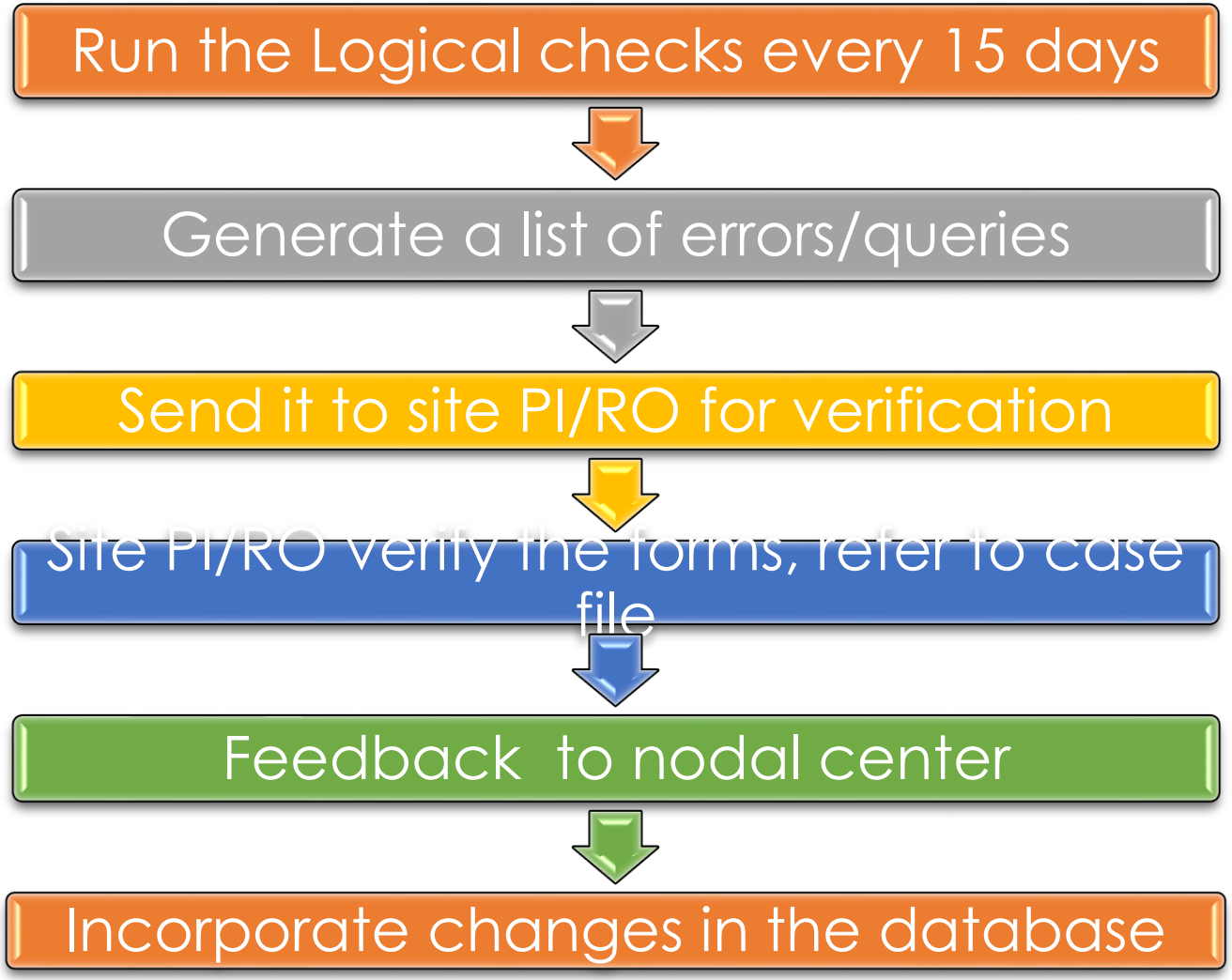
Diagnosis related checks

1. ‘Culture positive sepsis’ is YES but
   - no organism mentioned in form C or
   - antibiotic duration is <10 days and baby is discharged
2. Antibiotic duration >10 days but sepsis marked as NO

Checks related to dates, age, etc.

1. Date of discharge < DOB
2. If date of admission in NICU < DOB

Data cleaning by logical checks



Logical checks

Example

Labeled as culture positive sepsis but no organism exists in form C

enrlno	bname	dob	culposse p	Site RO /DEO's Remark	Nodal Centre's remark	Type of error	Correction in database
512	MANJU	05-May-11	Y	Clinical sepsis	"Clinical sepsis", - confirmed	Form Error	Set culpos='N' Set culneg='Y'
544	BABITA	06-May-11	Y	Clinical sepsis	"Clinical sepsis", - confirmed	Form Error	Set culpos='N'
955	GEETA	23-Jun-11	Y	Vanco + Amika (14d); discharged; bld cul-CONS (Form Cs not attached);Culture positive sepsis	"Culture positive sepsis" – orgm. CONS in bld cul.; to find form C hardcopy and also check in batch (form C database); if not found to re-enter	Others	First sample got entered (Previously It was not entered)
1028	SNTHOSH	28-Jun-11	Y	Ampi + genta x 2d; expired; blood cul sterile, CSF culture-Kleb. Clinical team decided- Culture positive sepsis	"Culture positive sepsis" – orgm. Klebsiella in bld cul.; to find form C hardcopy and also check in batch (form C database); if not found to re-enter	Others	CSF culture got entered (Previously CSF culture was not entered)

Summary: Quality assurance

- Meeting of PIs – every 8-12 weeks with defined objectives
- Developing consensus among site PIs; finalize SOP based on the consensus
- Strict adherence to SOPs
  - Innovative ways - **Quiz**
- Training of research staff
- Site visits!

ICMR Advanced Centre for Newborn Health Research

Team