Guidelines on prevention and control of infections in neonates

CONTENTS

ABBREVIATIONS AND GLOSSARY

CI	Confidence interval
CLD	Chronic lung disease
CPAP	Continuous positive airway pressure
ELBW	Extremely low birth weight
ES	Effect size
GDG	Guideline development group
GRADE	System for grading the quality of evidence and the strength of recommendations
kg	Kilogram
l	Litre
LBW	Low birth weight
MD	Mean difference
OR	Odds ratio
PICO	Population, intervention, comparison, outcome
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation
WMD	Weighted mean difference

EXECUTIVE SUMMARY

Neonatal sepsis is an important cause of morbidity and mortality, especially in low and middle-income countries. Infections contribute to 20.8% of neonatal mortality in India. (Sankar MJ, Neogi SB, Sharma J, Chauhan M, Srivastava R, Prabhakar PK, Khera A, Kumar R, Zodpey S, Paul VK. State of newborn health in India. Journal of Perinatology. 2016 Dec 7;36(s3):S3.) The morbidities related to neonatal infections include prolongation of hospital stay, increased cost of care, retinopathy of prematurity, periventricular leucomalacia, and abnormal neurodevelopmental outcomes.

Based on the timing of presentation, it is classified as early onset sepsis (EOS) for symptoms onset before 72 hours of birth, and as late onset sepsis (LOS) for symptoms beginning 72 hours after birth. EOS is related to maternal infection and LOS is often hospital acquired. Hospital/health care associated infections (HAIs) are potentially preventable but the available interventions vary from one setting to other. Various principles underline formulation of infection prevention and control strategies. These include, but not limited to antibiotic prophylaxis, decreasing use of invasive devices, improving hand hygiene practices, good house-keeping practices, improving nurse to patient ratio, human milk usage, probiotics, and kangaroo mother care.

The objective of this guideline is to improve the quality of care and outcomes for preterm and term infants by providing recommendations on the infection prevention and control strategies. The guideline development group identified 14 research questions to be of the highest priority for development of recommendations. For each question, the following four outcomes were considered to be critical: *mortality, hospital acquired infections, central line associated blood stream infections, and duration of hospital stay.* Benefits and harms in critical outcomes formed the basis of the recommendations for each question.

A separate search strategy was used for each of the priority questions to identify studies for inclusion in this review. At least two or more databases were searched to identify eligible studies. Search was restricted to studies in English language.

A standardized form was used to extract relevant information from studies. Systematically extracted data included: study identifiers, setting, design, participants, sample size, intervention or exposure, control or comparison group, outcome measures and results. The following quality characteristics were recorded for all randomized controlled studies: allocation concealment, blinding of intervention, loss to follow up, and intention to treat analysis. Standard methods were for quality assessments for observational studies.

We used a GRADE approach for assessing the quality of evidence and the recommendations. The quality of the set of included studies reporting results for an outcome was graded as: high, moderate, low or very low.

The strength of a recommendation reflects the degree of confidence that the desirable effects of adherence to a recommendation outweigh the undesirable effects. The decisions were made on the basis of evidence of benefits and harms; quality of evidence; values and preferences of policy-makers, health-care providers and parents; and whether costs are qualitatively justifiable relative to benefits in low- and middle- income countries.

Each recommendation was graded as ***strong*** when there was confidence that the benefits clearly outweigh the harms, or ***weak*** when the benefits probably outweigh the harms, but there was uncertainty about the trade-offs. A strong or weak recommendation was further classified as ***situational*** if the benefits outweigh the harms in some situations but not in others. For example, some

recommendations were considered relevant only to settings where resources were very limited while others were considered relevant only to settings where certain types of facilities were available.

Guideline Development Group

The Clinical Practice guideline (CPG) for the prevention and control of infecitons in

None of the members of this CPG group declared any conflicts of interest.

Scope og guidelines:

Target audience

The primary audience for this guideline includes health-care professionals (pediatricians, nurses and other practitioners) who are responsible for delivering care for neonates in different levels of heath care as well health programme managers and policymakers in all settings. The information in this guideline will be useful for developing job aids and tools for training of health professionals to enhance their delivery of neonatal care. These guidelines may also be used by health policymakers to set up facilities in special care newborn units for optimal care of infants.

Population of interest

The guidelines focus on the use of non-invasive respiratory support namely, CPAP, HFNC and NIPPV among term and preterm neonates admitted to healthcare settings with various respiratory conditions in low- and middle-income countries.

Priority questions:

1. In mothers with PROM, does antibiotic use compared to no antibiotics, decrease incidence of EOS (in <72 hours of life) in neonates?
2. In delivery room, does adherence to 6 cleans decrease the incidence of neonatal HAIs?
3. In neonates admitted in NICU, does CLABSI bundle approach compared to routine care decrease the incidence of CLABSI?

4. In neonates admitted in NICU, does VAP bundle approach compared to routine care decrease the incidence of VAP?
5. In neonates admitted in NICU, does ANTT approach compared to routine care decrease the incidence of HAI?
6. In neonates admitted to neonatal unit, what interventions can result in improved compliance to hand hygiene?
7. In neonatal units, is hand rub as effective as hand wash in decreasing neonatal infections?
8. In neonatal ICUs, does optimising nurse to patient ratio decrease the incidence of HAI?
9. In neonatal units, does education of health care workers and patients result in reduced HAIs?
10. In neonatal units, does adherence to antibiotic stewardship policies result in decreased incidence of HAI?
11. In neonates, does family centered care compared to routine care decrease the incidence of HAI?
12. In neonatal units, does active surveillance compared to no surveillance decrease the rate of HAIs?
13. In neonatal units, does environmental surveillance in presence of an epidemic, result in effective control of the epidemic?
14. In neonatal units, does routine environmental surveillance as compared to no surveillance decrease HAIs?
15. In neonatal units, does organism specific surveillance help in reducing the rates of HAI?

Critical outcomes and their definitions:

Outcomes	**Definition**
In-hospital mortality	All-cause death during the initial hospital stay
Hospital acquired infection (HAI)	Blood culture positive sepsis in neonates after 48 hours of hospital admission
CLABSI	*A CLABSI is a primary bloodstream infection (that is, there is no apparent infection at another site) that develops in a patient with a central line in place within the 48-hour period before onset of the bloodstream infection that is not related to infection at another site.*
VAP	Neonates who are mechanically ventilated for 48 h or more should have a new onset of abnormal chest radiographs and worsening of gas exchange (e.g. O2 desaturations, increased oxygen requirements, or increased ventilator demands) with at least three of the following criteria: temperature instability; new onset of purulent tracheal secretions, increased respiratory secretions with increased suctioning requirements, leukopenia [≤4000 white blood cells (WBC)/mm3] or leukocytosis (>15 000 WBC/mm3), apnea, tachypnea, retraction of chest wall, nasal flaring, grunting, wheezing, respiratory crackles, bradycardia

	(<100 beats/min), or tachycardia (>170 beats/min)
Duration of hospital stay	Duration in days from the day of admission to the day of discharge from the hospital

Recommendations:

Q1. Should CLABSI bundle versus routine care be used for reducing CLABSI in neonates admitted to NICU?

Objective

To evaluate if CLABSI insertion and mountainous care bundles reduce the incidence of CLABSI in neonates admitted to NICU

Methods

Participants

Infants admitted to NICU

Exposure

Central lines (Umbilical Venous Lines or Umbilical arterial lines or Peripheral inserted central catheters were inserted in the neonates for care and lasted for more than 48 hours.

Outcome

The primary outcome was the number of CLABSIs per 1000 central line or patient days.

A CLABSI is a primary bloodstream infection (that is, there is no apparent infection at another site) that develops in a patient with a central line in place within the 48-hour period before onset of the bloodstream infection that is not related to infection at another site. Culturing the catheter tip or peripheral blood is not a criterion for CLABSI.

Results

Literature search:

The last search was done in August 2019. The search term used was catheterization, central venous or adverse effects", "infection control or methods", "intensive care units", and "quality control" in PUBMED database and via the cross references of the most recent articles. It identified on systematic review published in *Arch Dis Child Fetal Neonatal Ed* 2017 and it included all manuscript on this subject in neonates from Jan 2010 to Jan 2017 and one article from India published after that. This guideline is based on the systematic review and did not include studies published after that.

1) Database searched: PUBMED
2) Date of search: 12-08-2019
3) Search strategy used:
   a) Step 1**:** The search term used was catheterization, central venous or adverse effects", "infection control or methods", "intensive care units", and "quality control"
   b) Step 2: Relevant cross-references from the retrieved articles (from the 1st step) including the latest articles published in year 2018 (Chakravarthy K et al. Indian Pedaitrics, July 2018) were searched
   c) Step 3: Also, the articles highlighted under the box 'similar articles' in Pubmed after entering the titles of eligible articles retrieved from step 1 and 2 were screened and evaluated if relevant.
4) Total number of new studies added: This guideline is based only on the systematic review published in *Arch Dis Child Fetal Neonatal Ed* 2017 and included 24 studies from the neonatal units.

The review identified 24 studies. The details are as follows:

Type of studies: Twenty-four studies were eligible for inclusion (table 2). While 5 studies described themselves as observational studies, all 24 studies were non-randomised intervention studies. No RCTs were found. Studies were excluded if they investigated a single intervention, were performed in adult or pediatric populations or were focused on a specific pathogen outbreak. Studies not published in English, and conference abstracts, were excluded.

Risk of bias: The mean NOS (new castle Ottawa scale) score across the studies was 7 (range 6–8) from a possible maximum of 9. Lower scores tended to be due to a lack of control for NNU centre and central line days, though all the observational studies controlled for birth weight and gestational age. In general, there was limited reporting of data collection and verification processes. Those studies reported as QI studies tended to have longer intervals between the before and after groups, and only two studies used interrupted time series analysis to account for temporal trends, with a further five studies using statistical process control.Using the SQUIRE reporting framework to assess the QI studies revealed that while the majority of studies provided detailed descriptions of the setting, the implementation process was not well documented. Few studies reported if the care bundle was implemented as intended (for instance, by measuring compliance with bundle elements), and no studies reported any unintended consequences.

Interventions and compliance

The most common technical elements included

- The use of a specific skin preparation protocol (79%)
- Maximal standard barrier precautions (71%)
- Daily assessment of the need for the central line (67%)
- Despite hand hygiene resulting in significant reductions in hospital acquired infections, practices were poorly described, with only four studies specifying a product for hand cleansing, and the remainder making reference only to ensuring appropriate hand hygiene. Hand hygiene audits were reported in only five (20%) of studies

The choice of skin disinfectant varied, with chlorhexidine gluconate and 70% isopropyl alcohol most commonly used (63%), though the strengths varied. Other preparations included povidone iodine (38%), or were unspecified (25%)..

The most common professional elements were

- Education and training (100%)
- Use of checklists (67%), and
- Audit and feed- back (63%).

Two studies attempted to associate specific elements with reductions in CLABSI rates, but were unable to isolate one single element. Bundle compliance was reported in seven (29%) studies, and ranged from 10% to 100%. Studies that reported initial lower compliance rates of 10%–30% generally reported improvement in rates over time. 5 out of 18 units did not submit compliance data.

Outcomes

The primary outcome was the number of CLABSIs per 1000 central line or patient days.

A CLABSI is a primary bloodstream infection (that is, there is no apparent infection at another site) that develops in a patient with a central line in place within the 48-hour period before onset of the bloodstream infection that is not related to infection at another site. Culturing the catheter tip or peripheral blood is not a criterion for CLABSI.

The Grade Table enlists the pooled effect of Bundle care on the outcome CLABSI

CLABSI rate using Bundle care

*24 observational studies reported this outcome. The quality of evidence is graded as high. Use of bundle approach reduces the rate of central line associated blood stream infections (***RR 0.40:** 0.31 to 0.51). i. e: **6 fewer per 1,000** (from 7 fewer to 5 fewer)

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Date: 23 August

Question: CLABSI bundle approach compared to routine care for decreasing incidence of CLABSI

Setting: in NICUs

Bibliography: Care bundles to reduce central line-associated bloodstream infections in the neonatal unit: a systematic review and meta-analysis Victoria

Payne,1 Mike Hall,2 Jacqui Prieto,1 Mark Johnson2,3: Arch Dis Child Fetal Neonatal Ed 2017;0:F1–F8.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CLABSI bundle approach	routine care	Relative (95% CI)	Absolute (95% CI)		
CLABSI rate (assessed with: a standard definition)												
24	observational studies	serious [a]	not serious	not serious	not serious	strong association	3.16/1000 (0.3%)	9.97/1000 (1.0%)	**RR 0.40** (0.31 to 0.51)	**6 fewer per 1,000** (from 7 fewer to 5 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Estimation of risk of bias in the 5 cohort studies by NewCastle Ottawa scale has shown problems with selection of non-exposed cohort and comparability of controls for NICU care and central line days

Summary of Evidence

Bundle care to reduce CLABSI rate

There is high quality evidence from observational studies that Bundle care both for initiation and maintenance of central lines decreases the incidence of CLABI rate, when compared to no bundle care in neonates with central lines in situ for

48 hours or more. The components of the bundle approach were not uniform and there is significant variation across the studies.

Summary of Recommendations

QUESTION

Should CLABSI bundle approach vs. routine care be used for decreasing incidence of CLABSI?	
POPULATION:	decreasing incidence of CLABSI
INTERVENTION:	CLABSI bundle approach
COMPARISON:	routine care
MAIN OUTCOMES:	CLABSI rate;
SETTING:	in NICUs
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Neonatal intensive care unit (NICU) CLABSI rates ranged from 1.3 to 24.1 cases per 1000 central line days in Neoantal Intensive Care Units	

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Infection is an important cause of morbidity and mortality in NICUs. Significant reduction in CLABSI rates is likely to improve overall neonatal outcomes and also result in reduced NICU stay and thereby the costs. Need for expertise and appropriate use of Central lines is an important practice variation. The evidence from observational studies support that CLABSI bundles result in **6 fewer CLABSI per 1,000 catheter days** (from 7 fewer to 5 fewer) . There are no reported undesirable effects on CLABSI bundle implementation.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	Infection is an important cause of morbidity and mortality in NICUs. Significant reduction in CLABSI rates is likely to improve overall neonatal outcomes and also result in reduced NICU stay and thereby the costs. Need for expertise and appropriate use of Central lines is an important practice variation. The evidence from observational studies support that CLABSI bundles result in **6 fewer CLABSI per 1,000 catheter days** (from 7 fewer to 5 fewer) . There are	

	no reported undesirable effects on CLABSI bundle implementation.	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ● High ○ No included studies	There is 5 to 7 fewer CLABSI rates for 1000 catheter days in units that implement the CLABSI bundle	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	All units which implement CLABSI bundle have shown reduced CLABSI rates irrespective of the baseline risk or rate. However there is a wide variation in the components on the CLABSI bundle and also in the compliance rates of each bundle component	

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	The cost of bundle approach or the implementation of CLABSI bundle is more of behaviour and policy change and hence there are no undesirable effect of introduction of CLABSI bundle	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ● Large savings ○ Varies ○ Don't know	The resource requirements for the initiation and maintainence bundle does not pose any additional burden on the cost of care. However in an adult study that evaluated QI program to reduce CLABSI sugessted for every CLABSI prevented, the programme costs $5404 and suggested that it is cost saving when compared with the cost of an infection (which ranges from $6000 to over $56 000) which implies a cost saving of 1: 1.2 to 1: 10. (Herzer KR, Niessen L, Constenla DO, Ward WJ Jr, Pronovost PJ. Cost-effectiveness of a quality improvement programme to reduce central line-associated bloodstream infections in intensive care units in the USA. *BMJ Open*. 2014;4(9):e006065. Published 2014	

	Sep 25. doi:10.1136/bmjopen-2014-006065)	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ● Low ○ Moderate ○ High ○ No included studies	In an adult study that evaluated QI program to reduce CLABSI sugessted for every CLABSI prevented, the programme costs $5404 and suggested that it is cost saving when compared with the cost of an infection (which ranges from $6000 to over $56 000) which implies a cost saving of 1: 1.2 to 1: 10.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ No included studies	Yes the current evidence favors the intervention in comparison to the routine care	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact	As the cost of implementation and the resource requirement is low, improvign the implementation	

○ Probably increased ● Increased ○ Varies ○ Don't know	strategies would result in lower CLABSI across all settings.	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Although at the outset the bundle approach is a an accepatable method by all care givers, there is a wide variation in the components of the bundle and also in the compliance rates suggesting the need for continued and sustained efforts for implementation of all interventions	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Although at the outset the bundle approach is a an accepatable method by all care givers, there is a wide variation in the components of the bundle and also in the compliance rates suggesting the need for continued and sustained efforts for implementation of all interventions	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	**High**			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	**Large savings**	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the	Probably favors the intervention	**Favors the intervention**	Varies	No included studies

	JUDGEMENT						
			comparison				
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	**Increased**	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

CONCLUSIONS

Recommendation

There is a high grade quasi- experimental evidence that care bundles reduce CLABSIs in the NNU. However, there is variation in the list of bundle elements. We recommended the CDC checklist for implementation of Care bundles in

Neonatal Intensive care units.

Justification

Although the quality of evidence is from observational stuides, every CLABSI is an additional burden on the already overburdened NICU in LMIC and MICs. As the compliance improves the reduction in CLABSI would drop

Subgroup considerations

We did not consider any subgroups for this as we felt the approach is equally effective for all neonates on central lines

Implementation considerations

Checklists, Education, Staff motivation and Leadership by the nurses would play a key role in improving the compliance to CLABSI bundle care.. A checklist from CDC is appended with the guideline.

Monitoring and evaluation

A constant monitoring of compliance and CLABSI with uniform definitons is needed to ensure the efforts are constant and sustained. A CDC tool for monitoring and definition of CLABSI is appended

Research priorities

The bundle components that result in the maximum reduciton in CLABSI and the external validity of these bundle components need to be tested in future studies.

Checklist for Prevention of Central Line Associated Blood Stream Infections

Based on 2011 CDC guideline for prevention of intravascular catheter-associated bloodstream infections:
https://www.cdc.gov/infectioncontrol/guidelines/bsi/index.html
Strategies to Prevent Central Line–Associated Bloodstream Infections in Acute Care Hospitals: 2014 Update
http://www.jstor.org/stable/10.1086/676533

For Clinicians:

Follow proper insertion practices

Perform hand hygiene before insertion.
Adhere to aseptic technique.
Use maximal sterile barrier precautions (i.e., mask, cap, gown, sterile gloves, and sterile full body drape).
Choose the best insertion site to minimize infections and noninfectious complications based on individual patient characteristics.
- ☐ Avoid femoral site in obese adult patients.

Prepare the insertion site with >0.5% chlorhexidine with alcohol.
Place a sterile gauze dressing or a sterile, transparent, semipermeable dressing over the insertion site.
For patients 18 years of age or older, use a chlorhexidine impregnated dressing with an FDA cleared label that specifies a clinical indication for reducing CLABSI for short term non-tunneled catheters unless the facility is demonstrating success at preventing CLABSI with baseline prevention practices.

Handle and maintain central lines appropriately

Comply with hand hygiene requirements.
Bathe ICU patients over 2 months of age with a chlorhexidine preparation on a daily basis.
Scrub the access port or hub with friction immediately prior to each use with an appropriate antiseptic (chlorhexidine, povidone iodine, an iodophor, or 70% alcohol).
Use only sterile devices to access catheters.
Immediately replace dressings that are wet, soiled, or dislodged.
Perform routine dressing changes using aseptic technique with clean or sterile gloves.
- ☐ Change gauze dressings at least every two days or semipermeable dressings at least every seven days.
- ☐ For patients 18 years of age or older, use a chlorhexidine impregnated dressing with an FDA cleared label that specifies a clinical indication for reducing CLABSI for short-term non-tunneled catheters unless the facility is demonstrating success at preventing CLABSI with baseline prevention practices.

Change administrations sets for continuous infusions no more frequently than every 4 days, but at least every 7 days.
- ☐ If blood or blood products or fat emulsions are administered change tubing every 24 hours.
- ☐ If propofol is administered, change tubing every 6-12 hours or when the vial is changed.

Promptly remove unnecessary central lines

Perform daily audits to assess whether each central line is still needed.

For Healthcare Organizations:

Educate healthcare personnel about indications for central lines, proper procedures for insertion and maintenance, and appropriate infection prevention measures.
Designate personnel who demonstrate competency for the insertion and maintenance of central lines.
Periodically assess knowledge of and adherence to guidelines for all personnel involved in the insertion and maintenance of central lines.
Provide a checklist to clinicians to ensure adherence to aseptic insertion practices.
Reeducate personnel at regular intervals about central line insertion, handling and maintenance, and whenever related policies, procedures, supplies, or equipment changes.
Empower staff to stop non-emergent insertion if proper procedures are not followed.
Ensure efficient access to supplies for central line insertion and maintenance (i.e. create a bundle with all needed supplies).
Use hospital-specific or collaborative-based performance measures to ensure compliance with recommended practices.

Supplemental strategies for consideration:

Antimicrobial/Antiseptic impregnated catheters
Antiseptic impregnated caps for access ports

Q2. Should VAP bundle versus routine care be used for reducing ventilation Associated Pneumonia in neonates admitted to NICU?

Objective

To evaluate if VAP care bundles reduce the incidence of **Ventilation Associated Pneumonia** in neonates admitted to NICU

Methods

Participants

Infants admitted to NICU

Exposure

Patient is on mechanical ventilation for >2 calendar days on the date of event i.e VAP, with day of ventilator placement being Day 1.

Definitions

- VAP (CDC 2015): A pneumonia where the patient is on mechanical ventilation for >2 calendar days on the date of event, with day of ventilator placement being Day 1, * **AND** the ventilator was in place on the date of event or the day before. (If the ventilator was in place prior to inpatient admission, the ventilator day count begins with the admission date to the first inpatient location)
- VAP : Neonates who are mechanically ventilated for 48 h or more should have a new onset of abnormal chest radiographs and worsening of gas exchange (e.g. O2 desaturations, increased oxygen requirements, or increased ventilator demands) with at least three of the following criteria: temperature instability; new onset of purulent tracheal secretions, increased respiratory secretions with increased suctioning requirements,

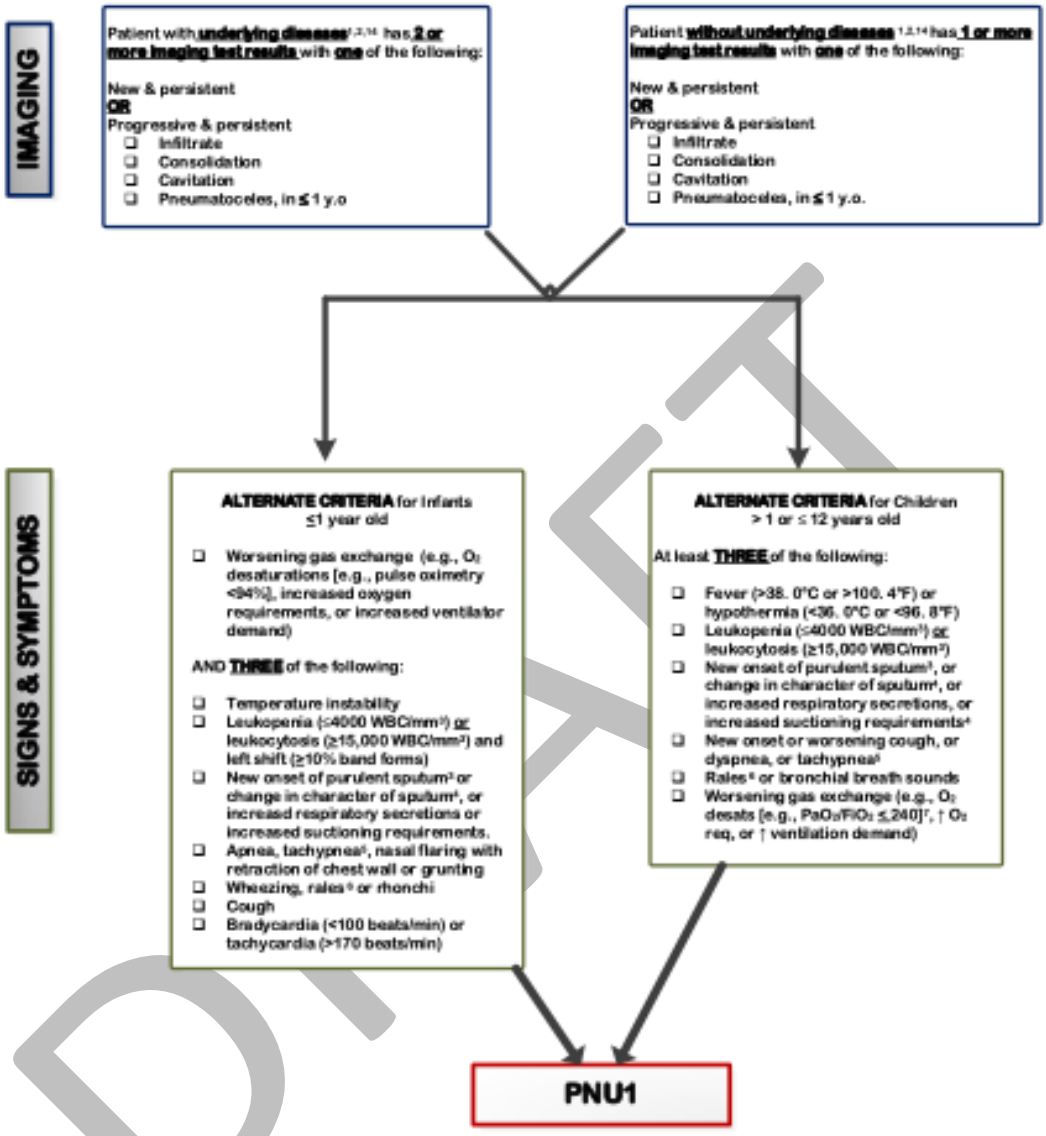
leukopenia [≤4000 white blood cells (WBC)/mm3] or leukocytosis (>15 000 WBC/mm3), apnea, tachypnea, retraction of chest wall, nasal flaring, grunting, wheezing, respiratory crackles, bradycardia (<100 beats/min), or tachycardia (>170 beats/min) [9].

Chest radiographs are considered the backbone of VAP diagnosis as the initial diagnosis is based on clinical suspicion and the presence of new radiographic changes 48h after the initiation of ventilation [10]. The CDC defined these changes as the presence of at least one of the following: a new or progressive and persistent (>24 h) infiltrate, consolidation, cavitation, or pneumatoceles in two or more serial chest radiographies

- Pneumonia (CDC 2015): Algorithm attached
- The VAP rate is calculated as the number of VAP infections identified per 1000 ventilator days (VAP cases ÷ ventilator days × 1000) among all intubated patients
- The length of mechanical ventilation is counted as the number of days a patient had a ventilator need.
- Hospital stay is the number of days the patient spent in the NICU.

Figure 2: Pneumonia Flow Diagram, Alternative Criteria for Infants and Children

Facility ID#_____**Event #**_____ **Event Date** __/__/____



Outcome

The primary outcome was the number of VAP cases per 1000 ventilation days.

Results

Literature search:

The last search was done in September 2019. We identified a systematic review on this topic published in June 2019 in J Spec Pediatr Nurs. 2019; e12264. It evaluated the impact of ventilator bundles on the incidence of ventilator-associated pneumonia in mechanically ventilated neonates and children in intensive care units. This systematic review was conducted using the key computerized databases (CINAHL, Medline, Embase and Cochrane) as well as additional sources, with no publication date limitations, and extensively searched till January 2018. Inclusion criteria focused on ventilator bundles used in mechanically ventilated neonates and children aged from 0 to 18 years. This search identified 8 studies but only two relevant to neonatal patients. An updated search by us identified another two studies on same subject by us.

The review identified 4 studies. The details are as follows:

Type of studies: Four studies were eligible for inclusion (table 2). Two studies were before and after observational studies and two were quality improvement projects. No RCTs were found. All the studies used the same definition for VAP and evaluated the VAP rate per 1000 ventilation days as the primary outcome. In one of the studies the baseline rate is not available. The Interventions differed in each of the studies. One study reported only the VAP rates in subgroup and not in the cohort as a whole.

Grading of Evidence

All are single centre studies. Data collection was over a period of 4 years in one of the QI study. As all were observational or QI studies the certainty of evidence for each of the outcomes was started with a low grade evidence.

Quality of included studies

Author(year)	Population relevant And described appropriately	All patients evaluated	Interventions appropriate and compliance measures	Outcomes all measured and objective	Controlled for gestational age, birth weight, duration of ventilation and sickness	Appropriate statistical analysis	Total
Tayel (2017)	1	2	1	2	0	2	8
Azab (2015)	2	2	1	2	0	1	8
Cebellos	1	0	1	1	0	1	4
Pepin	1	0	1	1	0	1	4

2 studies of medium quality and 2 studies are of low quality: Maximum quality score=12; 0–4 points were considered low quality, 5–8 points were considered medium quality and 9–12 points were considered as high quality.

Reduction in VAP rate

- Dose response effect was not reported in the four studies evaluated.
- The effect was large in 2 of the 4 studies with p value <0.001
- The effect was more significant when applied to infants at lower gestation as in the study by Pepin 2019 and effect was significantly more when applied to units with high VAP rates.

As 2 of the 3 criteria for upgrading evidence was present from the eligible studies, for reduction in VAP rates, there is moderate grade evidence from observational studies that VAP bundle reduces VAP rates.

Duration of Mechanical ventilation

Two of the four studies reported reduction in the days of mechanical ventilation. MV days in VAP cases reduced from 47 to 33 days in the QI study by Pipen et al

and 21.50 ± 7.6 days in baseline period to 10.36 ± 5.2 days during the QI period in the study by Azeb et al.

The effect size appears reasonable and the effect is more when the duration of baseline is more.

Duration or length of hospital stay

Two of the four studies reported in a reduction of length of hospital or NICU days with the isntroduction of VAP bundle..

Azab et al: Reduction days from 23.9 ± 10.3 versus 22.8 ± 9.6 days with introduction of VAP bundle

Pipen et al: LOS reduced in VAP cases from 136 to 100 days with introduction of VAP bundle approach

The effect size appears reasonable and the effect is more when the duration of baseline is more.

Mortality

Only one study reported reduction in the mortality with the introduction of VAP bundle.

(Azeb et al…25 % versus 17.3 %)

Interventions

The most common technical elements included in the VAP bundle in neonates were classified as below

1. Minimize exposure to pathogens
    a. Strict hand hygiene
    b. Universal gloving
    c. Limit circuit breaks

    d. Replace stand by circuits with new tubing if patient required reintubation

2. Intubation
    a. Intubation equipment maintained as cealn as possible during intubation attempts (sterile fields)
    b. Ensuring the ET tube is properly positioned every 3 to 4 hours
3. Extubation readiness
    a. Ventilation weaning protocols
    b. use of CPAP or Non-invasive ventilation
4. Oral Care
    a. Palate protectors cleaned every shift
    b. Oral suctioning prior to ET suctioning
    c. Single use oral suction catheters
    d. Maintain oral hygiene with colostrum or mothers own milk every shift
    e. Do not use bulb suction
5. Equipment management
    a. Head end elevation by 30
    b. Resuscitation bags to be replaced every week
    c. Separate catheter for oral and ET suction

Question

Should VAP bundle approach vs. routine care be used for decreasing incidence of VAP?	
Population:	decreasing incidence of VAP
Intervention:	VAP bundle approach
Comparison:	routine care
Main outcomes:	New outcome;
Setting:	neonates on invasive ventilation
Perspective:	
Background:	
Conflict of interests:	

Assessment

Problem Is the problem a priority?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	VAP is the second most common healthcare-associated infection which accounts for 22.7% of these infections in paediatric intensive care units (PICUs). According to the National Healthcare Safety Network report, VAP rates varied between 0.2/1,000 ventilator days to 0.8/1,000 ventilator days in the US PICUs in 2012 (Dudeck et al., 2013). A point-prevalence survey of hospital-acquired infections and anti- microbial use carried out in Ireland in 2012 revealed that 20% of all nosocomial pneumonias were associated with intubation of respira- tory tract and ventilation. Mortality rates associated with VAP range between 20% and 70% worldwide.	
Desirable Effects How substantial are the desirable anticipated effects?		
Judgement	Research evidence	Additional considerations
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	VAP bundle approach is known to reduce the VAP rates, reduce duration of mechanical ventilation, duration hosptial stay and also mortality among newborns with VAP. However the effects on the these outcomes are variable and the effect is more significant when the rate of VAP is more. The components of VAP bundle are variable and the implementation of each component of VAP bundle is a challenge in resource poor settings.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
Judgement	Research evidence	Additional considerations

○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	VAP bundle approach is known to reduce the VAP rates, reduce duration of mechanical ventilation, duration hosptial stay and also mortality among newborns with VAP. However the effects on the these outcomes are variable and the effect is more significant when the rate of VAP is more. The components of VAP bundle are variable and the implementation of each component of VAP bundle is a challenge in resource poor settings.	
Certainty of evidence What is the overall certainty of the evidence of effects?		
Judgement	Research evidence	Additional considerations
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Study One: VAP rate reduced from 24.6 to 19.9 per 1000 ventilaiton days Study Two; VAP rate reduced from 36.4 to 23 per 1000 ventilation days Study Three: VAP rate reduced from 6.2 to 0 per 1000 ventilation days in the subgroup of patients with birth weight 1000 to 1500 grams Study Four: VAP rate was 2.2 per 1000 ventilation days post bundle approach	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
Judgement	Research evidence	Additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	VAP bundle implementaion is a quality measures and likely to be acceptable across all settings.	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Judgement	Research evidence	Additional considerations

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	There are no possible undesirable effects of introduction of VAP bundle	
Resources required How large are the resource requirements (costs)?		
Judgement	Research evidence	Additional considerations
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ● Large savings ○ Varies ○ Don't know	Two studies that measured the cost savings associated with the implementation of ventilator bundles in the NICU and PICU (Brilli et al., 2008; Ceballos et al., 2013). Brilli et al. (2008) conducted their retrospective case-control study with the aim to explore the financial impact of VAP in PICU patients. The VAP attributable cost of 51,157USD per patient was reported in the study. Moreover, the authors concluded that the implementation of a ventilator bundle resulted in a decrease of hospital costs by $2,353,222. Ceballos et al. (2013) displayed estimated cost savings of $300,000 post imple- mentation of a ventilator bundle in the NICU.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
Judgement	Research evidence	Additional considerations
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Implementation of VAP bundle would require good nurse patient ratio, availablity of endotracheal tubes, disposable circuits, suction cathters, and mothers own milk	

Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ No included studies	Two studies that measured the cost savings associated with the implementation of ventilator bundles in the NICU and PICU (Brilli et al., 2008; Ceballos et al., 2013). Brilli et al. (2008) conducted their retrospective case-control study with the aim to explore the financial impact of VAP in PICU patients. The VAP attributable cost of 51,157USD per patient was reported in the study. Moreover, the authors concluded that the implementation of a ventilator bundle resulted in a decrease of hospital costs by $2,353,222. Ceballos et al. (2013) displayed estimated cost savings of $300,000 post imple- mentation of a ventilator bundle in the NICU.	
Equity What would be the impact on health equity?		
Judgement	Research evidence	Additional considerations
● Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	As Bundle approach is likely to be more effective in settings with high incidence of VAP, this approach is useful for all settings and very cost effective.	
Acceptability Is the intervention acceptable to key stakeholders?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	It would require constant training, motivation and auditing of the bundle components	

Feasibility Is the intervention feasible to implement?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The interventions of bundle approach are feasible and one needs work in improving the compliance of the interventions	

Summary of judgements

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable Effects	Trivial	Small	**Moderate**	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	**Trivial**		Varies	Don't know
Certainty of evidence	Very low	Low	**Moderate**	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	**Large savings**	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	**Moderate**	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	No included studies
Equity	**Reduced**	Probably	Probably no	Probably	Increased	Varies	Don't

	Judgement						
		reduced	impact	increased			know
Acceptability	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Feasibility	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

Conclusions

Recommendation

There is moderate grade evidence from observational studies that implementation of VAP bundle would improve the VAP rates, duration of mechanical ventilation and duration of hospital stay. There is low grade evidence from observational studies it would reduce mortality

Justification

Subgroup considerations

No subgroup considerations are made. VAP bundle is a useful approach for all neonates on mechanical ventilation

Implementation considerations

Althoug VAP bundle would reduce the VAP rates, the components of the bundle and the compliance to implemtation of VAP Bundle components are widely

variable and there is a need to popularize the most acceptable bundle components

Monitoring and evaluation

Auditing of compliance to BUndle components should be regular QI activity across all NICUs that do neonatal ventilation

Research priorities

There is further need for more organized QI studies in neonatal populations to develop the most accetable VAP Bundle approach

Q3. What is the effect of using hand rub (alcohol based) versus hand wash for hand hygiene in Neonatal units on infection rates and mortality?

Research questions

Among neonates being managed in neonatal units, does

- Replacing hand wash with hand rub result in increased risk of hospital acquired infections?

Objectives

Among neonates managed in neonatal units, what is the impact of using hand rub instead of hand wash (where ever it is indicated e.g., at entrance to NICU, visibly soiled hands, etc) on hospital acquired infections?

Methods

Participants

Preterm (<37 weeks) and term neonates (<28 days) admitted to neonatal units in hospital setting

Interventions

Intervention: Randomized controlled trials or observational studies

Control: Where hand wash is used as indicated

***Outcomes and their definitions*:**

The following table provides the list of critical outcomes and their definitions.

Importance:

CRITICAL- Mortality, Hospital acquired infections (HAI), Central line related blood stream infections (CLABSI), duration of hospital stay

IMPORTANT- costs involved, adherence to hand hygiene, adverse skin effects of hand hygiene

LIMITED IMPORTANCE- process measures e.g., compliance to ANTT measures

Table 1: Definition of key outcomes

Outcomes	**Definition**
In hospital mortality	All-cause death during the hospital stay
Hospital acquired infections (HAI)	Neonatal infections (pneumonia/ sepsis/ meningitis) acquired after 72 hours of life
CLABSI	• Recognized pathogen in one or more blood specimens (culture or nonculture based microbiologic methods), performed for clinical diagnostic or therapeutic purposes and not related to infection at another site • Commensal organism (e.g., coagulase-negative staphylococci, diphtheroids, bacillus, viridans streptococci, aerococcus, micrococcus, propionibacterium), identified from two or more blood specimens obtained on separate instances (culture or nonculture based microbiologic methods), performed for clinical diagnostic or therapeutic purposes and not related to infection at another site AND at least one of the following signs (1) fever (temperature >38.0°C), (2) hypothermia (temperature <36.0°C), or (3) apnea or bradycardia • Central line or umbilical catheter in place for more than 2 days and • Central line in place on day of or day before CLABSI diagnosis
Duration of hospital stay	Duration of hospital stay from birth/admission to discharge
Cost of care	Costs involved in patient care including total expenditure incurred to patient, insurance company and government, if any

Results

We have searched PubMed and Cochrane CENTRAL using the same search strategy from January 2000 to July 2019. A total of 95 studies were identified, 46

from PubMed and 49 from Cochrane CENTRAL. Of these, 3 studies were found to be eligible for inclusion in the review.

Table 2: Search strategy

Database	Terminology	Limits	Studies identified
PubMed	"Hand rub" AND ("hand wash" OR scrub)	01-01-2000 to 31-07-2019	46
Cochrane CENTRAL	"Hand rub" AND ("hand wash" OR scrub)	01-01-2000 to 31-07-2019	49
Related articles and references search			3

Table 3: Summary of included studies

S No	Author, year	Study population and setting	Formulations compared	CFU before	CFU after	Sepsis rates (before and after)	Mortality (before and after)
1	Sharma et al, 2013	Level III NICU 35 nurses	1- Plain soap hand washing for 15 sec 2- alcohol hand rub (propanol) 3- 0.5% povidone Iodine scrub for 15 sec	Median (IQR) 1- 158.7 ±129; 105 (31-300) 2- 161.8 ±122; 150 (31-300) 3- 145.4 ±128; 89 (25-300)	Median (IQR) 1- 60 (10, 300); absolute decrease: 15 (0,103); % decrease: 33.3 (0,82) 2- 8 (0, 60); absolute decrease: 100 (15,235); % decrease: 92 (67,100) 3- 10.5 (0, 100.5); absolute decrease: 40 (1.5,159); % decrease: 87 (40,100)	NA	NA

2	Larson, 2005	2 NICUs in Manhattan- 43 and 50 bedded. Sequential crossover design	1. Hand washing- antiseptic detergent containing 2% CHG 2. hand rub- 61% ethanol & emollients	Mean (log_{10}) 1. 3.47 2. 3.47	Mean (log_{10}) 1. 3.21 2. 3.11	1. 181/1,516 neonates; 245/25,735 exposure days	2. 190/1,426 neonates; 314/26,025 exposure days
3	Kac, 2005	50 HCWs from various wards. Crossover design	1. Hand wash- unmedicated soap, 30 sec 2. Hand rub- 45% 2-propanol, 30% 1-propanol, 0.2% mecetronium ethylsulphate and emollients, 30 sec	Geometric mean CFU (95% CI) 1. 61 (44-85) for palm; 66 (47-93) for finger tips 2. 66 (43-101) for palm; 61 (40-93) for finger tips	Geometric mean CFU 1. 16 (10-25) for palm; 12 (7-18) for finger tips 2. 2 (1-3) for palm; 2 (1-3) for finger tips		

Pooled effects of key outcomes

The GRADE table (see below) enlists the effect size for the available key outcomes for the comparison of aseptic non touch technique with routine care.

Hospital Acquired Infection rates: One study in NICU has measured infection rates. The infection rates were 9.5 episodes per 1,000 patient days in hand washing period compared to 12.1 episodes per 1,000 patient days. The number of neonatal admissions in hand washing period were 1,516 and hand rub period were 1,416.

CLABSI rates: One study in NICU has measured central line associated infection rates. The infection rates were 14.8 episodes per 1,000 central venous catheter days in hand washing period compared to 18.2 episodes per 1,000 central venous catheter days. The number of neonatal admissions in hand washing period were 1,516 and hand rub period were 1,416.

VAP rates: One observational study has shown that ventilator associated pneumonia rates were 1.7 per 1,000 ventilation days in hand washing period and 2.2 per 1,000 patient days in hand rub period. The number of neonatal admissions in hand washing period were 1,516 and hand rub period were 1,416.

In-hospital mortality: None of the studies have reported this outcome

Duration of hospital stay: None of the studies have reported this outcome

Hand hygiene compliance: None of the studies have reported this outcome

Adverse effects related to hand hygiene: One observational study has studied self-reported and observer assessed skin condition. Hand rubs were shown to have better scores in both the ways, indicating lesser adverse effects with hand rubs.

Bacterial load reduction: One observational study has shown that mean bacterial counts (log_{10}) reduced from 3.47 to 3.11 in hand washing period, and from 3.47 to 3.21 in hand rub period. Another study has shown that mean CFU (geometric mean) reduced from 61 (44-85) to 16 (10-25) for palm and from 66 (47-93) to 12 (7-18) for finger tips with hand washing. With hand rub, it reduced from 66 (43-101) to 2 (1-3) for palm and 61 (40-93) to 2 (1-3) for finger tips. The third study has shown 33.3% reduction in median CFU with hand wash and 92% reduction with hand rub. Although the data cannot be pooled, hand rub has higher reduction in bacterial load as compared to hand wash.

Author(s): Rajendra Prasad, Srinivas Murki, Venkataseshan S, Tejo Pratap, Avneet Kaur, Kamal Arora
Date: 2/10/19
Question: Hand Rub compared to Hand Wash in in neonates for prevention of infections
Setting: Neonatal units

Certainty assessment							**№ of patients**		**Effect**		**Certainty**	**Importance**
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Hand Rub**	**Hand Wash**	**Relative (95% CI)**	**Absolute (95% CI)**		
Hospital acquired infections (assessed with: culture)												
1	observational studies	not serious	not serious	not serious	not serious	none	314/26025 (1.2%)	245/25735 (1.0%)	OR 0.98 (0.77 to	0 fewer per 1,000 (from 2 fewer	⊕⊕⊕⊕ HIGH	CRITICAL

									1.25)	to 2 more)		
Central line associated blood stream infections (assessed with: culture)												
1	observational studies	not serious	not serious	not serious	not serious	none	167/9169 (1.8 %)	131/8830 (1.5 %)	OR 0.99 (0.77 to 1.33)	0 fewer per 1,000 (from 3 fewer to 5 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Ventilator associated pneumonia (assessed with: culture)												
1	observational studies	not serious	not serious	not serious	not serious	none	10/4465 (0.2 %)	7/4049 (0.2 %)	OR 1.61 (0.55 to 5.44)	1 more per 1,000 (from 1 fewer to 8 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Bacterial load reduction (assessed with: % reduction of CFU)												
1	observational studies	not serious	not serious	not serious	not serious	none	92	33.3	-		⊕⊕⊕⊕ HIGH	IMPORTANT

CI: Confidence interval;
OR: Odds ratio

Question

Should Hand Rub vs. Hand Wash be used for in neonates for prevention of infections?	
Population:	in neonates for prevention of infections
Intervention:	Hand Rub
Comparison:	Hand Wash
Main outcomes:	Hospital acquired infections; Central line associated blood stream infections; Ventilator associated pneumonia; Bacterial load reduction;

Setting:	Neonatal units
Perspective:	
Background:	
Conflict of interests:	

Problem Is the problem a priority?		
Judgement	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There is always a confusion on the superiority of Hand wash with Hand rubs in intensive care units. Hand wash has been traditionally used in health care settings. But, hand rubs have shown to improve compliance and reduce bacterial load better. (Andreas F. Widmer, Replace Hand Washing with Use of a Waterless Alcohol Hand Rub?, *Clinical Infectious Diseases*, Volume 31, Issue 1, July 2000, Pages 136–143)	
Desirable Effects How substantial are the desirable anticipated effects?		
Judgement	**Research evidence**	**Additional considerations**
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Repeated hand wash could lead to skin breakdown. The compliance rates with hand wash are low compared to hand rub. Lack of emollients in hand rub would also cause similar problems. An increase in compliance to hand hygiene can significantly reduce health care associated infections. (Shlomai NO, Rao S, Patole S. Efficacy of interventions to improve hand hygiene compliance in neonatal units: a systematic review and meta-analysis. European Journal of Clinical Microbiology & Infectious Diseases. 2015 May 1;34(5):887-97.)	
Undesirable Effects How substantial are the undesirable anticipated effects?		
Judgement	**Research evidence**	**Additional considerations**

○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	Repeated hand wash could lead to skin breakdown. The compliance rates with hand wash are low compared to hand rub. Lack of emollients in hand rub would also cause similar problems. An increase in compliance to hand hygiene can significantly reduce health care associated infections. (Shlomai NO, Rao S, Patole S. Efficacy of interventions to improve hand hygiene compliance in neonatal units: a systematic review and meta-analysis. European Journal of Clinical Microbiology & Infectious Diseases. 2015 May 1;34(5):887-97.)	
Certainty of evidence What is the overall certainty of the evidence of effects?		
Judgement	**Research evidence**	**Additional considerations**
○ Very low ● Low ○ Moderate ○ High ○ No included studies	There is evidence from single observational study that the total infection rates, CLABSI and VAP rates are similar with hand wash and hand rub, bacterial counts were lesser with hand rubs, and adverse effects were less with hand rubs.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
Judgement	**Research evidence**	**Additional considerations**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Most studies have shown that the health care workers prefer hand rub over hand wash.	

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Judgement	**Research evidence**	**Additional considerations**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Although equivalent effects on reduction of infections, less adverse effects, ease of use and less time required favor the intervention	
Resources required How large are the resource requirements (costs)?		
Judgement	**Research evidence**	**Additional considerations**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	Waterless hand rub is less costly than traditional hand wash and required less time (147 $ for 1000 hand rub episodes versus 184$ for 1000 hand wash with Chlorhexidine hand wash). Nursing economics 2004; 22(4);196-99	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
Judgement	**Research evidence**	**Additional considerations**

○ Very low ○ Low ● Moderate ○ High ○ No included studies	Waterless hand rub is less costly than traditional hand wash and required less time (147 $ for 1000 hand rub episodes versus 184$ for 1000 hand wash with Chlorhexidine hand wash)	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
Judgement	**Research evidence**	**Additional considerations**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Waterless hand rub is less costly than traditional hand wash and required less time (147 $ for 1000 hand rub episodes versus 184$ for 1000 hand wash with Chlorhexidine hand wash)	
Equity What would be the impact on health equity?		
Judgement	**Research evidence**	**Additional considerations**
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	As hand hygiene compliance improves and cost reducuction can be achieved, hand rubs may be more likely to be used in low resource settings	
Acceptability		

Is the intervention acceptable to key stakeholders?		
Judgement	**Research evidence**	**Additional considerations**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	In summary, hand rubs require lesser time, have lesser costs, adverse effects and bacterial loads. All these features can make it an attractive first-line option for hand hygiene in neonatal units.	
Feasibility Is the intervention feasible to implement?		
Judgement	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Yes	

Summary of judgements

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	**Large**		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	**Trivial**		Varies	Don't know
Certainty of evidence	Very low	**Low**	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	**Moderate**	High			No included studies
Cost	Favors the	Probably	Does not	**Probably**	Favors the	Varies	No included

	Judgement						
effectiveness	comparison	favors the comparison	favor either the intervention or the comparison	**favors the intervention**	intervention		studies
Equity	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

Conclusions

Recommendation
Use of hand rubs is more effective than hand wash in reducing bacterial load and has lower adverse effects. But, this has not translated to decreased infection rates. In situations like entrance to an ICU and soiled hands, hand rub needs to be compared against hand wash for its effectiveness in future studies. Hand rub is recommended for routine hand hygiene, and hand wash is the current option for hand hygiene at entrance to ICU and when the hands are soiled.

Justification

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

Further studies should address

1. Hand rub vs hand wash on compliance rates
2. Hand rub vs hand wash on mortality
3. Hand rub vs hand wash at entrance to ICU
4. Hand rub vs hand wash when hands are soiled

Q4. What is the effect of interventions to improve hand hygeine in Neonatal units on Hand hygiene compliance, infection rates and mortality?

Research questions

Among neonates being managed in neonatal units, does

1. Interventions to improve hand hygiene increase hand hygiene compliance (HHC)?
2. Interventions to improve hand hygiene decrease hospital acquired infections (HAI)?
3. Interventions to improve hand hygiene decrease neonatal mortality?

Objectives

Among neonates managed in neonatal units, what is the impact of interventions to improve hand hygiene on key neonatal outcomes?

Which interventions improve hand hygiene compliance most effectively?

Methods

Methods and results will be discussed separately for each research question/objective.

Participants

Preterm (<37 weeks) and term neonates (<28 days) admitted to neonatal units in hospital setting

Interventions

Intervention: Quality improvement initiatives to improve hand hygiene compliance

Control: Baseline period before intervention was done

***Outcomes and their definitions*:**

The following table provides the list of critical outcomes and their definitions.

CRITICAL- Mortality, Hospital acquired infections, duration of hospital stay

IMPORTANT- improved hand hygiene, costs involved

LIMITED IMPORTANCE- decreased bacterial load

Outcomes	**Definition**
In hospital mortality	All-cause death during the hospital stay
Hospital acquired infections (HAI)	Neonatal infections (pneumonia/ sepsis/ meningitis) acquired after 72 hours of life
Sepsis	Clinical features of sepsis with or without isolation of organisms from blood/CSF/urine and laboratory parameters suggestive of sepsis
Duration of hospital stay	
Cost of care	Costs involved in patient care including total expenditure incurred to patient, insurance company and government, if any
Compliance to hand hygiene	Performing hand hygiene as indicated by WHO "5 moments for hand hygiene" (before touching a patient, before clean/aseptic procedures, after body fluid exposure/risk, after touching a patient, and after touching patient surroundings)

Results

We found one systematic review and meta-analysis that examined the effect of interventions to improve hand hygiene compliance on hand hygiene compliance *(Ofek Shlomai N, Rao S, Patole S. Efficacy of interventions to improve hand hygiene compliance in neonatal units: a systematic review and meta-analysis. Eur J Clin Microbiol Infect Dis. 2015 May;34(5):887-97)*. It had 16 observational studies publised till October 2013, and this meta-analysis was published in February 2015.

We updated the search by searching PubMed and Cochrane CENTRAL using the same search strategy from November 2013 to June 2019. A total of 156 additional citations were identified, 150 from PubMed and 6 from Cochrane CENTRAL. Of these, 13 studies were found to be eligible for inclusion in the review. Consequently, we updated the review, including studies from January 1 2000 to June 30 2019.

Table 1: Search strategy

Database	Terminology	Limits	Studies identified
PubMed	(("Hand Hygiene"[Mesh]) AND "Guideline Adherence"[Mesh]) AND "Intensive Care Units"[Mesh]	1-11-2013 to 31-06-2019	54
PubMed	(("Infant, Newborn"[Mesh]) OR "Intensive Care Units, Neonatal"[Mesh]) AND "Hand Hygiene"[Mesh]	1-11-2013 to 31-06-2019	96

Cochrane CENTRAL	(("Infant, Newborn") OR "Intensive Care Units, Neonatal") AND "Hand Hygiene"	1-11-2013 to 31-06-2019	3
Cochrane CENTRAL	(("Hand Hygiene") AND ("Guideline Adherence") AND "Intensive Care Units" in All Text	1-11-2013 to 31-06-2019	3

In the final analysis, we included 15 of the 16 studies included in the previous meta-analysis and 13 studies from updated search, making it a total of 28 observational studies. Of these, 21 studies provided data on change in hand hygiene compliance (13 older + 8 newer studies), 8 studies provided data on change in infection rates (6 older + 2 newer studies) and 2 studies provided data on change in mortality (1 newer + 1 older). Some studies have provided data of pre-intervention period, intervention period and post-intervention period. In such studies, intervention and post-intervention data was combined for analysis.

The various interventions done in individual studies are shown in table 1

S No	Author, year	Interventions
1	Sharek et al., 2002	1. Educational sessions 2. Notices 3. Reminder stickers on patient isolettes
2	Brown et al., 2003	1. Provision of alcohol-based hand rub, freestanding dispensers (stage 1) 2. Single mandatory education session 3. Personalised instruction in hand washing technique
3	Lam et al., 2004	1. Education sessions focusing on hand hygiene importance and techniques, plus face-to-face training sessions

		2. Hand hygiene protocols 3. Pictures of correct step-by-step hand washing placed on sinks 4. Alcohol-based hand rub available on each incubator 5. Clustering of handling and procedures
4	Won et al., 2004	1. Formal lectures on correct hand washing and importance of hand washing 2. Hand washing as part of orientation to all new staff 3. Labels with slogans placed throughout the nursery 4. Group feedback as well as private discussions with individual HCWs on errors in technique 5. Financial rewards and penalties according to hand washing performance 6. Public praise to good hand washers
5	Danchaivijitr et al., 2005 (MNMC hospital, Bangkok) Danchaivijitr et al., 2005 (Siriraj hospital, Bangkok)	1. Posters 2. Training 3. Performance feedback. Not clear if it was at a personal level or group feedback 4. Provision of alcohol-based hand rub 1. Posters 2. Leaflets 3. Rewarding HCWs who suggest the most attractive name for the alcohol gel and a hand washing slogan, parade to boost hand hygiene practice 4. Not clear if performance feedback was given
6	das Neves et al., 2006	1. Musical parodies on hand hygiene, put on hospital radio >1/shift 2. Artistic information posters 3. Phrases on hand hygiene, by hospital radio
7	Pessoa-Silva et al., 2007	1. Reminders in the form of posters 2. Focus group sessions to provide education as well as group

		feedback 3. A member of the research team provided advice regularly on clean care
8	Raskind et al., 2007	Ongoing promotion programme, illustrations and written information regarding correct techniques: 1. E-mailed brochure 2. Prominently displayed bulletins 3. Posters 4. Verbal reminders
9	Picheansathian et al., 2008	Hand hygiene promotion programme including 1. A training session 2. Regular performance feedback 3. Reminder poster displays 4. Provision of bedside alcohol-based solution 5. The distribution of individual bottles of alcohol-based hand rub 6. Supply of hand towels was increased to meet the need of all working shifts
10	Gill et al., 2009	1. Training session 2. Regular performance feedback at both individual and group levels 3. Reminder poster displays 4. Bedside alcohol-based solution 5. Supply of individual bottles of alcohol-based rub and hand towels
11	Helder et al., 2010	Education programme including: 1. Overview of nosocomial infections and prevention 2. Instructions for optimal hand hygiene procedures 3. Performance feedback on hand washing was received automatically by the HCW because only sufficiently rubbed parts will glow in UV light

		4. Senior healthcare professionals were encouraged to serve as role models
12	van den Hoogen et al., 2011	1. Questionnaire regarding unit's hand washing protocol 2. Direct feedback from observer to the observed person. After observation, the HCW had to fill in a questionnaire and received immediate feedback 3. Informing HCWs of baseline hand washing rates 4. Informing HCWs of nosocomial infection rates 5. Videos of common mistakes on all computers in the unit 6. Posters with cartoons showing correct hand washing, changing every 3 weeks 7. Special attention to hand hygiene in new staff orientation
13	Helder et al., 2012	1. Computer screen saver displays instead of static poster. Messages included images of hands, germs and disinfection methods 2. Screen saver message designs changed every 2 weeks to avoid desensitisation
14	Mazi et al., 2013	1. Lectures 2. Hands-on workshop 3. Exhibitions 4. Three-monthly audit and feedback to team leaders and hospital director
15	Mukerji et al., 2013	1. E-Learning package 2. Posters 3. Screen savers
16	Mahfouz et al, 2014	Multi modal interventions 1. Consultation and advocacy meetings 2. Intensifying the provision of alcohol based rub 3. Training and Education 4. Intensifying use of reminders in the work place 5. Involvement of hospital leaders in HH activities

		6. Evaluation and feedback 7. Provision and insurance of a continuous supply of soaps and paper towels through regular daily rounds by infection control practitioners
17	Chhapola et al, 2014	3 strategies 1. Education and training 2. Reminders- demonstration and posters 3. Audit and feedback
18	Biswal et al, 2014	1. Educational sessions 2. Demonstration of HH techniques- videos and ultraviolet gel technology. 3. Posters from the WHO and banners 4. Promoting use of alcohol-based handrub 5. Provision of soap and alcohol handrub
19	Barahona-Guzman et al, 2014	INICC multidimensional hand hygeine approach 1. Administrative support 2. Supplies availability 3. Education and training 4. Reminders in the workplace 5. Process surveillance 6. Performance feedback.
20	Helder et al, 2014	Phase 1: Education program Phase 2: Gain-framed screen saver messages, Infection prevention week, Promotion of consistent glove use
21	Rosenthal et al, 2015	INICC multidimensional hand hygeine approach 1. Administrative support 2. Supplies availability 3. Education and training 4. Reminders in the workplace 5. Process surveillance 6. Performance feedback.

22	Sadeghi-Moghaddam et al, 2015	1. Educational program 2. Regular supply of anti-septic solution
23	Kramer et al, 2017	Shortened hand rub time from 30 sec to 15 sec
24	Chandonnet et al, 2017 QI study	Educating parents and family members using 1. Education sheets in multiple languages, posters and stickers 2. Real-time feedback 3. Easy access to supplies needed for HH 4. Visual display of HH compliance reports
25	Ram et al, 2017	By female behaviour change communicators 1. Didactic sessions, role plays, and field pilots Delivered over 16 days.
26	Kallam et al, 2018	1. Creating a hand hygiene training course 2. Reinforcing hand hygiene practices at staff meetings 3. Visual reminders and 4. Securing an adequate supply of clean towels for hand drying
27	Phan et al, 2018	Education programme consisting of 1. 10-min video outlining the reasons for hand hygiene, 2. small group discussion about the reasons for hand hygiene, 3. a role-playing game where participants had to identify pathogens using an ultraviolet light on participants hands to determine if the hands had been washed, 4. small group (5–7 participants) discussion to determine the 5 moments of hand hygiene, 5. practice and discussion of procedural aspects of hand washing technique - six steps of hand hygiene 6. lecture about the efficacy of alcohol-based hand-rub compared to water and soap handwashing.
28	Hoang et al, 2018	1. Video didactic triggered by motion sensor to play above wash basin 2. Surveillance camera placed over hand washing area

		3. Hand swabbing and culture

Summarising interventions:

Use of visual aids- 17

Educational sessions (theory)- 15

Training personnel (practical)- 10

Provision of hand rubs- 12

Performance feedback- 12

Audit/using unit data for feedback- 4

Others: Protocols, Rewards and incentives, Punishments, Process surveillance, Video didactic teaching, Shortening hand-rub time from 30 sec to 15 sec

Pooled effects of key outcomes

The GRADE table (see below) enlists the effect size for the available key outcomes for the comparison of interventions to improve HHC vs. no interventions to improve HHC.

Hand hygiene compliance: Twenty one studies involving 63,930 observations of hand hygeine reported this outcome. The quality of evidence was graded as *low*. There was a significant increase in the compliance to hand hygiene compliance before and during/after the intervention (RR 1.42; 95% CI 1.40 to 1.44). The number of properly performed hand hygiene events increased by 187 more per 1,000 (from 179 more to 196 more)

Hospital acquired infections: Eight studies reported this outcome. The number of neonates involved is not mentioned, and data was reported as infection rates per 1,000 patient days. The quality of evidence was graded as *high*. The risk of having an infection significantly decreased (RR 0.57; 95% CI: 0.45 to 0.71). The infection rates during intervention and post-intervention periods decreased by 11 per 1,000 patient days (95% CI: 7, 14).

In-hospital mortality: Two studies involving 3,028 neonates and 3 neonatal units reported this outcome. The quality of evidence was graded as *high*. There was significant decrease in mortality during/after the interventions (RR: 0.54; 95% CI: 0.48 to 0.61). The neonatal deaths have decreased by 162 per 1,000 neonates (95% CI: 138, 183)

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Date: 2/10/19

Question: Impact of interventions to improve hand hygiene in neonatal units for prevention of infections

Setting: Neonatal units

Certainty assessment							No of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**interventions to improve HHC**	**no interventions**	**Relative (95% CI)**	**Absolute (95% CI)**		
HHC compliance												
21	observational studies	not serious	serious [a]	not serious	not serious	publication bias strongly suspected [b]	21406/34170 (62.6%)	13282/29760 (44.6%)	**RR 1.42** (1.40 to 1.44)	**187 more per 1,000** (from 179 more to 196 more)	⨁⨁◯◯ LOW	IMPORTANT
Infection rates per 1,000 patient days (all)												
8	observational studies	not serious	not serious	not serious	not serious	none	113/8000 (1.4%)	199/8000 (2.5%)	**RR 0.57** (0.45 to 0.71)	**11 fewer per 1,000** (from 14 fewer to 7 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Mortality												
2	observational studies	not serious	not serious	not serious	not serious	none	286/1497 (19.1%)	540/1531 (35.3%)	**RR 0.54** (0.48 to 0.61)	**162 fewer per 1,000** (from 183 fewer to 138 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL

CI: Confidence interval; **OR:** Odds ratio; **RR:** Risk ratio

Explanations

a. The I2 value is 97% indicating unexplained heterogeneity

b. In the funnel plot, most of the studies are seen outside the funnel region, and studies with small sample size are inappropriately low

Question

Should interventions to improve hand hygiene compliance (HHC) vs. no interventions be used for improving HHC in neonatal units?	
Population:	**improving HHC in neonatal units**
Intervention:	**interventions to improve hand hygiene compliance (HHC)**
Comparison:	**no interventions**
Main outcomes:	**HHC compliance; Infection rates per 1,000 patient days (all); HHC compliance; Infection rates per 1,000 patient days (all); Mortality;**
Setting:	**Hospital**
Perspective:	
Background:	
Conflict of interests:	

Assessment

Problem Is the problem a priority?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Health care acquired infections (HCAI) significantly increase mortality, morbidity, length of hospitalization (by several weeks), cost of care (1.4 fold increase) and long term neurodevelopmental abnormalities (1.4 fold increase). Their incidence ranges from 3.6-60/1,000 admissions. Meticulous hand hygeine is the single most important intervention to decrease HCAIs. Reported hand hygeine compliance rates are 30-40% in ICUs. The interventions are easy to design, but difficult to implement.	
Desirable Effects How substantial are the desirable anticipated effects?		
Judgement	Research evidence	Additional considerations
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Decreased healthcare infections results in decreased mortality, morbidity and costs of care Undesirable effects- related to increased work load on health care team. But overall sickness level bound to decrease.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
Judgement	Research evidence	Additional considerations

○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	Decreased healthcare infections results in decreased mortality, morbidity and costs of care Undesirable effects- related to increased work load on health care team. But overall sickness level bound to decrease.	
Certainty of evidence What is the overall certainty of the evidence of effects?		
Judgement	Research evidence	Additional considerations
○ Very low ○ Low ○ Moderate ● High ○ No included studies	Based on the available data, the certaility of evidence is high for decreased infection rates and mortality. The certainity of evidence is low for improving hand hygeine compliance	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
Judgement	Research evidence	Additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important	The outcomes of mortality and infection rates are rated as CRITICAL, and hand hygeine compliance as IMPORTANT	

uncertainty or variability		
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	The desirable effects of decreased mortality and infection rates far outweigh the potential adverse effects related to the intervention. However, the adverse effects have not been well studied. These can include increased workload and stress levels among healthcare workers	
Resources required How large are the resource requirements (costs)?		
Judgement	Research evidence	Additional considerations

○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ● Large savings ○ Varies ○ Don't know	Interventions increasing HH compliance from a 10% baseline to ≥20% are likely to be cost-effective solely through reduced MRSA-BSI. Increasing compliance from 10% to 40% was estimated to cost US$2515 per 10,000 bed-days with 3.8 QALYs gained in a paediatric ICU (PICU) and US$1743 per 10,000 bed-days with 3.7 QALYs gained in an adult ICU. If baseline compliance is not >20%, the intervention is always cost-effective even with only a 10% compliance improvement.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
Judgement	Research evidence	Additional considerations
○ Very low ○ Low ○ Moderate ● High ○ No included studies	As summarised below, the evidence is very clear that cost savings outweigh investments.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison	Interventions increasing HH compliance from a 10% baseline to ≥20% are likely to be cost-effective solely through reduced MRSA-BSI. Increasing compliance from 10% to 40% was estimated to cost US$2515 per 10,000 bed-days with 3.8 QALYs gained in a paediatric ICU (PICU) and US$1743 per 10,000 bed-days with 3.7 QALYs gained in an adult ICU. If baseline compliance is not >20%, the intervention is always cost-effective	

○ Probably favors the intervention ● Favors the intervention ○ Varies ○ No included studies	even with only a 10% compliance improvement. (Luangasanatip N, Hongsuwan M, Lubell Y, Limmathurotsakul D, Srisamang P, Day NP, Graves N, Cooper BS. Cost-effectiveness of interventions to improve hand hygiene in healthcare workers in middle-income hospital settings: a model-based analysis. Journal of Hospital Infection. 2018 Oct 1;100(2):165-75.). The evidence from studies conducted in various intensive care units from Korea showed that the economic savings outweighed costs by a ratio of 5.08. This means for every 1,000 ruppes invested, a saving of 5,080 ruppes can be expected. (Chun JY, Seo HK, Kim MK, Shin MJ, Kim SY, Kim M, Kim CJ, Song KH, Kim ES, Lee H, Kim HB. Impact of a hand hygiene campaign in a tertiary hospital in South Korea on the rate of hospital-onset methicillin-resistant Staphylococcus aureus bacteremia and economic evaluation of the campaign. American journal of infection control. 2016 Dec 1;44(12):1486-91.)	
Equity What would be the impact on health equity?		
Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ● Increased ○ Varies ○ Don't know	Improved hand hygeine compliance will be more effective in sicker neonates in NICU who undergo more frequent handling and more invasive procedures. Also, it will have more impact on neonates in NICU than stable babies roomed in with mother.	
Acceptability		

Is the intervention acceptable to key stakeholders?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	As discussed within the group, the need for these interventions and their acceptability is very high.	
Feasibility Is the intervention feasible to implement?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	From the various studies included in the review, it is clear that these interventions can be successfully applied. Moreover, these interventions succeeded in improving hand hygeine compliance levels. Certain studies which continued surveillance beyond the study period showed that the improvements in hand hygeine and decrease in infections persisted with continued effects.	

Summary of judgements

	Judgement						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	●

CONCLUSIONS

RECOMMENDATION

Interventions to improve hand hygiene compliance should be instated in all neonatal units to improve hand hygiene compliance (LOW quality, STRONG recommendation), to decrease hospital acquired infection rates (HIGH quality, STRONG recommendation) and decrease mortality (HIGH quality, STRONG recommendation).

JUSTIFICATION

Hand hygiene compliance: Twenty one studies involving 63,930 observations of hand hygiene reported this outcome. The quality of evidence was graded as *low*. There was a significant increase in the compliance to hand hygiene compliance before and during/after the intervention (RR 1.42; 95% CI 1.40 to 1.44). The number of properly performed hand hygiene events increased by 187 more per 1,000(from 179 more to 196 more)

Hospital acquired infections: Eight studies reported this outcome. The number of neonates involved is not mentioned, and data was reported as infection rates per 1,000 patient days. The quality of evidence was graded as *high*. The risk of having an infection significantly decreased (RR 0.57; 95% CI: 0.45 to 0.71). The infection rates during intervention and post-intervention periods decreased by 11 per 1,000 patient days (95% CI: 7, 14).

In-hospital mortality: Two studies involving 3,028 neonates and 3 neonatal units reported this outcome. The quality of evidence was graded as *high*. There was significant decrease in mortality during/after the interventions (RR: 0.54; 95%

CI: 0.48 to 0.61). The neonatal deaths have decreased by 162 per 1,000 neonates (95% CI: 138, 183)

SUBGROUP CONSIDERATIONS

None

IMPLEMENTATION CONSIDERATIONS

Implementing these interventions requires constant efforts from nurses, clinicians and administrators. The benefits associated with this approach (available literature and units own data) can be used to convince the hospital administration for promoting such interventions

MONITORING AND EVALUATION

Sustained monitoring and evaluation is the key as the effects of quality improvement initiatives can rapidly wean off if not monitored.

RESEARCH PRIORITIES

Further research is unlikely to give additional information on the impact of interventions in decreasing hospital acquired infection rates and mortality. However, further research is likely to identify the effect of each of the observed interventions (e.g., Education, Audio-Visual aids, Hands on Training, Incentives and punishments, Video didactic teaching, Provision of hand rubs and towels, and giving performance feedback and auditing) on improving hand hygiene compliance.

Q5. What is the effect of using aseptic non touch technique (ANTT) in Neonatal units on infection rates and mortality?

Research questions

Among neonates being managed in neonatal units, does

- Using aseptic non touch technique (ANTT) decrease hospital acquired infections (HAI)?
- Using aseptic non touch technique (ANTT) decrease neonatal mortality?

Objectives

Among neonates managed in neonatal units, what is the impact of using aseptic non touch technique (ANTT) on key neonatal outcomes?

Methods

Participants

Preterm (<37 weeks) and term neonates (<28 days) admitted to neonatal units in hospital setting

Interventions

Intervention: Quality improvement initiatives using aseptic non touch technique (ANTT)

Control: Baseline period before intervention was done

Outcomes and their definitions:

The following table provides the list of critical outcomes and their definitions.

Importance:

CRITICAL- Mortality, Hospital acquired infections (HAI), Central line related blood stream infections (CLABSI), duration of hospital stay

IMPORTANT- costs involved

LIMITED IMPORTANCE- process measures e.g., compliance to ANTT measures

Table 1: Definition of key outcomes

Outcomes	Definition
In hospital mortality	All-cause death during the hospital stay
Hospital acquired infections (HAI)	Neonatal infections (pneumonia/ sepsis/ meningitis) acquired after 72 hours of life
CLABSI	• Recognized pathogen in one or more blood specimens (culture or nonculture based microbiologic methods), performed for clinical diagnostic or therapeutic purposes and not related to infection at another site • Commensal organism (e.g., coagulase-negative staphylococci, diphtheroids, bacillus, viridans streptococci, aerococcus, micrococcus, propionibacterium), identified from two or more blood specimens obtained on separate instances (culture or nonculture based microbiologic methods), performed for clinical diagnostic or therapeutic purposes and not related to infection at another site AND at least one of the following signs (1) fever (temperature >38.0°C), (2) hypothermia (temperature <36.0°C), or (3) apnea or bradycardia • Central line or umbilical catheter in place for more than 2 days and • Central line in place on day of or day before CLABSI diagnosis
Duration of hospital stay	Duration of hospital stay from birth/admission to discharge

Cost of care	Costs involved in patient care including total expenditure incurred to patient, insurance company and government, if any

Results

We have searched PubMed and Cochrane CENTRAL using the same search strategy from January 2000 to June 2019. A total of 47 studies were identified, 43 from PubMed and 4 from Cochrane CENTRAL. Of these, only 1 study was found to be eligible for inclusion in the review.

Table 2: Search strategy

Database	Terminology	Limits	Studies identified
PubMed	"aseptic non touch technique" OR ANTT	01-01-2000 to 31-06-2019	43
Cochrane CENTRAL	"aseptic non touch technique" OR ANTT	01-01-2000 to 31-06-2019	4

Summary of included studies

Author/ year	Setting, design	HAI rates	CLABSI rates	Hospital stay	Mortality	Compliance to ANTT
Khurana, 2017	NICU, India Quality improvement	* 19.9 per 1,000 patient days → 15.3 per 1,000 patient days * 235/2,132 admissions → ?? * 279/14,019 patient days → ??	NA	NA	NA	Use of procedure tray/trolley (23/143 → 55/111), Pre-procedure hand hygiene (95/143 → 82/111) Correct glove use (91/143 → 77/111) IV hub scrubbing (0/28 → 12/20), Local skin cleaning (16/49 → 18/27), PPPE use (22/40 → 28/35) and disposal (11/40 → 18/35), Main aseptic field used (81/143 → 71/111) Key parts protected when not in use (61/143 → 60/111) Use of non-touch technique (71/143 → 78/111), Reduction in key part contamination (64/143 → 35/111)
Gerceker, 2017	48 PHO patients with central lines, Turkey RCT	NA	2/21 patients (ANTT) and 9/16 (routine care)	NA	NA	NA

			2/1,051 catheter days → 9/887 catheter days			
Clare, 2018	Improvement in staff competencies with training in ANTT method	NA	NA	NA	NA	Pre-procedure hand hygiene (17/49 → 48/49) Correct glove use (39/49 → 46/49) Key-part protection (15/49 → 41/49) Non-touch technique (27/49 → 49/49) Key-part cleaning (0/49 → 40/49)
Flynn, 2015	Patients >18 years, receiving BMT Retrospective cohort	NA	3/71 patients (ANTT) → 1/77 (sterile) 3/2,501 catheter days →1/2,182 catheter days	NA	NA	NA

Pooled effects of key outcomes

The GRADE table (see below) enlists the effect size for the available key outcomes for the comparison of aseptic non touch technique with routine care.

Hospital Acquired Infection rates: One study in NICU has measured infection rates. The infection rates decreased from 19.9 episodes per 1,000 patient days to 15.3 episodes per 1,000 patient days.

CLABSI rates: Two studies reported this outcome- 1 is a randomized controlled trial and another is a retrospective study. These studies were not conducted in neonates, resulting in an indirect evidence. The quality of evidence was graded as *low*. The risk of having a CLABSI was shown to be reduced in the RCT- 10.1/1,000 catheter days to 1.9/1,000 catheter days (p=0.026) and not shown to be different in the retrospective study- 0.46/1,000 catheter days to 1.2/1,000 catheter days (p=0.357).

In-hospital mortality: None of the studies have reported this outcome

Compliance to ANTT procedures: Two studies reported this outcome, 1 from neonates and another based on pragmatic evaluation using mixed methods approach. These studies provided a low-quality evidence that ANTT training improves pre-procedure hand hygiene, key-part protection, and use of non-touch technique; moderate quality evidence that ANTT training does not improve glove use; and high-quality evidence that ANTT training improved cleaning of key-parts.

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Date: 08-09-2019

Question: Aseptic non touch technique (ANTT) compared to routine practices for decreasing HAIs, mortality, CLABSI rates

Setting: neonatal units

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ANTT**	**routine practices**	**Relative (95% CI)**	**Absolute (95% CI)**		
pre-procedure hand hygiene												
2	observational studies	not serious	serious [a]	serious [b]	not serious	none	130/160 (81.3%)	112/192 (58.3%)	RR 1.40 (1.21 to 1.63)	233 more per 1,000 (from 122 more to 367 more)	⊕⊕◯◯ LOW	IMPORTANT
correct glove use												
2	observational studies	not serious	not serious	serious [b]	not serious	none	123/160 (76.9%)	130/192 (67.7%)	RR 1.12 (0.99 to 1.27)	81 more per 1,000 (from 7 fewer to 183 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
key-part protection												
2	observational studies	not serious	serious [c]	serious [b]	not serious	none	101/160 (63.1%)	76/192 (39.6%)	RR 1.59 (1.28 to 1.98)	234 more per 1,000 (from 111 more to 388 more)	⊕⊕◯◯ LOW	IMPORTANT
non touch technique use												
2	observational studies	not serious	serious [d]	serious [b]	not serious	none	127/160 (79.4%)	98/160 (61.3%)	RR 1.29 (1.12 to 1.50)	178 more per 1,000 (from 74 more to 306 more)	⊕⊕◯◯ LOW	IMPORTANT
key-part cleaning												
2	observational studies	not serious	not serious	serious [b]	not serious	very strong association	52/69 (75.4%)	0/77 (0.0%)	RR 59.78 (8.14 to 438.97)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT

CI: Confidence interval; RR: Risk ratio

Explanations

a. I2 = 95%

b. one of these studies was conducted in a non-neonatal population

c. I2 = 89%

d. I2 = 90%

Question

Should aseptic non touch technique (ANTT) vs. routine practices be used for decreasing HAIs?	
Population:	decreasing HAIs
Intervention:	aseptic non touch technique (ANTT)
Comparison:	routine practices
Main outcomes:	pre-procedure hand hygiene; correct glove use; key-part protection; non touch technique use; key-part cleaning;
Setting:	neonatal units
Perspective:	
Background:	
Conflict of interests:	

Assessment

Problem Is the problem a priority?		
Judgement	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Health care acquired infections (HCAI) significantly increase mortality, morbidity, length of hospitalization (by several weeks), cost of care (1.4 fold increase) and long term neurodevelopmental abnormalities (1.4 fold increase). Their incidence ranges from 3.6-60/1,000 admissions. Aseptic Non Touch Technique deals with key part and key site protection and use of an aseptic field. Employing ANTT can standardize the procedures and potentially result in decreased HCAIs	
Desirable Effects How substantial are the desirable anticipated effects?		
Judgement	**Research evidence**	**Additional considerations**
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Decreased healthcare infections results in decreased mortality, morbidity and costs of care Undesirable effects- related to increased work load on health care team. But overall sickness level bound to decrease.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
Judgement	**Research evidence**	**Additional**

		considerations
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	Decreased healthcare infections results in decreased mortality, morbidity and costs of care Undesirable effects- related to increased work load on health care team. But overall sickness level bound to decrease.	
Certainty of evidence What is the overall certainty of the evidence of effects?		
Judgement	**Research evidence**	**Additional considerations**
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Based on the available data, there is high quality evidence that ANTT approach improves key part cleaning, moderate quality evidence that ANTT approach improves correct gove use and low quality evidence that ANTT approach improves pre-procedure hand hygiene, key-part protection and non-touch technique use. There is data from single study in NICU that it decreases infection rates. There is data from 2 studies that CLABSI rates are reduced.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
Judgement	**Research evidence**	**Additional considerations**
○ Important uncertainty or variability	The team of experts has reviewed the outcomes of mortality, HCAI, CLABSI rates and duration of hospital stay as critical. Costs involved is rated as	

○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	important, and process measures are rated as less important	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Judgement	**Research evidence**	**Additional considerations**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	The desirable effects of decreased mortality and infection rates far outweigh the potential adverse effects related to the intervention. However, the adverse effects have not been well studied. These can include increased workload and stress levels among healthcare workers	
Resources required How large are the resource requirements (costs)?		

Judgement	Research evidence	Additional considerations
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ● Large savings ○ Varies ○ Don't know	The resources needed relate to time of the personnel (trainers, nurses and administration), organising simulation sessions, and monitoring adherence to protocols. There is no published data assessing cost-effectiveness of these interventions	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
Judgement	**Research evidence**	**Additional considerations**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	There are no studies which studies the required resources	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
Judgement	**Research evidence**	**Additional considerations**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the	The costs involved in implementing an ANTT approach may relate to the simulation sessions. However, the benefits include standardization of common procedures, very large benefit from decreasing HCAIs and CLABSI rates.	

intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ No included studies		
Equity What would be the impact on health equity?		
Judgement	**Research evidence**	**Additional considerations**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ● Increased ○ Varies ○ Don't know	There is need for standardization of procedures in NICUs. Although it is easy to acheive in units with better nurse-patient ratio, it is more important and difficult to achieve in high turnover settings. The ANTT approach serves as an aid to help standardising the common day-to-day procedures like intubation, IV cannulation, IV fluid administration and ET suction.	
Acceptability Is the intervention acceptable to key stakeholders?		
Judgement	**Research evidence**	**Additional considerations**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	All the new interventions have the problem of facing inherent tendency of a system of 'not to change'. When introduced with collaboration of nurses, administrators and other team members, these can be successfully incorporated into the existing protocols.	

Feasibility Is the intervention feasible to implement?		
Judgement	**Research evidence**	**Additional considerations**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The studies done in NICU and various other setups has shown that ANTT can improve compliance with aseptic precautions and decrease mortality.	

Summary of judgements

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	**Large**		Varies	Don't know
Undesirable Effects	Large	Moderate	**Small**	Trivial		Varies	Don't know
Certainty of evidence	Very low	**Low**	Moderate	High			No included studies
Values	Important	Possibly	Probably no	**No**			

	Judgement						
	uncertainty or variability	important uncertainty or variability	important uncertainty or variability	**important uncertainty or variability**			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	**Large savings**	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			**No included studies**
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the	Probably favors the intervention	**Favors the intervention**	Varies	No included studies

	Judgement						
			comparison				
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	**Increased**	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**

Conclusions

Recommendation
ANTT approach should be incorporated into NICU protocols related to common procedures like feeding, IV cannulation, IV fluid preparation and administration, intubation, ET suction to decrease infection rates (LOW quality, WEAK

recommendation), CLABSI rates (LOW quality, WEAK recommendation) and improving compliance to aseptic procedures (MODERATE quality, STRONG recommendation).

Justification

The GRADE table (see below) enlists the effect size for the available key outcomes for the comparison of aseptic non touch technique with routine care.

Hospital Acquired Infection rates: One study in NICU has measured infection rates. The infection rates decreased from 19.9 episodes per 1,000 patient days to 15.3 episodes per 1,000 patient days.

CLABSI rates: Two studies reported this outcome- 1 is a randomized controlled trial and another is a restrospective study. These studies were not conducted in neonates, resulting in an indirect evidence. The quality of evidence was graded as *low*. The risk of having a CLABSI was shown to be reduced in the RCT- 10.1/1,000 catheter days to 1.9/1,000 catheter days (p=0.026) and not shown to be different in the retrospective study- 0.46/1,000 catheter days to 1.2/1,000 catheter days (p=0.357).

In-hospital mortality: None of the studies have reported this outcome

Compliance to ANTT procedures: Two studies reported this outcome, 1 from neonates and another based on pragmatic evaluation using mixed methods approach. These studies provided a low quality evidence that ANTT training improves pre-procedure hand hygiene, key-part protection, and use of non-touch technique; moderate quality evidence that ANTT training does not improve glove use; and high quality evidence that ANTT training improved cleaning of key-parts.

Subgroup considerations

None

Implementation considerations

Implementing these interventions requires constant efforts from nurses, clinicians and administrators. The benefits associated with this approach (available literature and units own data) can be used to convince the hospital administration for promoting such interventions

Monitoring and evaluation

Sustained monitoring and evaluation is the key as the effects of quality improvement initiatives can rapidly wean off if not monitored.

Research priorities

More studies need to be conducted to study effects of ANTT approach on HCAI rates, CLABSI rates, mortality and resource utilization for implementing ANTT in neonatal units.

Q6: In neonatal units, does organism specific surveillance help in reducing HAI?

Objectives

To evaluate the effect of organism specific surveillance to reduce HAI in neonatal units

Participants

Infants admitted in NICU

Exposure

Organism specific surveillance

Outcome

MRSA colonization was classified as either prevalent (initial MRSA screen positive at admission) or as incident (subsequent MRSA screen positive after a negative initial screen).

Outcomes and their definitions

The following table provides the list of critical outcomes and their definitions.

Outcomes	**Definition**
In hospital mortality	All-cause death during the hospital stay
Hospital acquired infections	Neonatal infections (pneumonia/ sepsis/ meningitis) acquired after 48 hours of admission
Sepsis	Clinical features of sepsis with or without isolation of organisms from blood/CSF/urine and laboratory parameters suggestive of sepsis

Colonization	MRSA or MSSA grown from sites like nasal orifice, skin or anal area without any clinical features suggestive of sepsis anytime during the NICU stay

5) Database searched: PUBMED
6) Date of search: 17-08-2019
7) Search strategy used:

d) Step 1**:** The search term used was catheterization, central venous or adverse effects", "surveillance", "organism specific", "neonates "and "infections". With this search we could not get any relevant articles (total articles retrieved were 52; similar articles are also searched'

e) Step 2: We looked for the individual organisms. Methicillin resistant *Staphylococcal aureus is known for its virulence and high mortality and morbidities in NICU.* We used following search words "MRSA", "neonates", "active surveillance'' and "HAI". With this we were able to retrieve 34 articles. When we used additional filter for humans, we got 28 articles.

f) Step 3: Also, the articles highlighted under the box 'similar articles' in PUBMED after entering the titles of eligible articles retrieved from step 1 and 2 were screened and evaluated if relevant.

We critically reviewed each article. Finally, we included 10 relevant articles. All the studies are observational studies. One has used simulation model (Goldstein et al.).

Summary of included studies

S.No	Study details	Intervention	Control	Outcomes
1.	Bharadwaj et al 2019(1) QI initiative	Post and sustenance period 1. Enhancing staff awareness and effecting change in the attitude to infection control practices through education 2. Providing easy availability of cleaning equipment 3. Scripting a standard protocol and admission workflow for outborns 4. Increasing awareness on IPC policies among parents and visitors	Pre intervention Data was collected	Colonization 3.3 vs 1.2 vs 1.3 per 1000 days (3/909 vs 2/1666 vs 4/3076) Outcomes HO-MRSA acquisition cases from neonatal admissions – 0 vs 0 2. Days free of HO-MRSA (days-0) among neonatal unit admissions - NA 3. HH compliance of health care staff involved in care (process indicator). 93.7 (87.1 -97.1) vs 100 (88-100) vs 100 4. Environmental hygiene compliance in the neonatal unit (process indicator). - 82.2% (71.4%-95%) vs 91.3% (76.9%-94.7%) vs 100 (75-100%)
2	Geraci et al 2014(2) Prospective study	Environmental surveillance Cohorting		Colonization – 88/4356 vs 34/3864 vs 65/4952 Acquisition: 20.2 vs 8.8 vs 13.2 per 1000 days Clinical infection: 5.2 vs 6.5

	N=722			vs 4.9 per 1000 days
3	Karchmer et al 2002(3) Outbreak control Cost effective analysis		Prevalence of colonization 40%	Overall cost of surveillance cultures during this outbreak was $27 589.73. Attributable excess cost of $17 422 for MRSA (as compared with MSSA) bacteraemia To prevent 75 BSI and 4 deaths - $1 306 600
4	Goldstein 2018(4) N= 53 in each epoch	Surveillance once in 4 weeks	Surveillance once in a week	Mean number (95% CI) of colonization: 2.9 (1.2 -5.4) vs 0.6 (0.2-1) Mean (95% CI) duration of colonization: 307 (90-540) vs 61 (18-128) days
5	Kaushik et al 2015(5) Before and after study	Surveillance Single nasal swab at admission N=1576	Nil N=1512	MRSA BSI related deaths: 0 vs 1 MRSA BSI: 3.8 vs 5.3 per 1000 patients During intervention phase: None of non-colonized babies had BSI Direct screening cost was $208 per patient. Since 28 neonates had to be screened to detect one colonization, $5,824 was estimated per

				detection.
6	Victor O.Poopola et al 2016(6) Before and after study Organism - MSSA Retrospective	Active surveillance and decolonization 1195 neonates 22045 patient days 8999 were screened 89 were tested positive on screen 78.7% were treated with mupirocin for decolonization	No policy for the same 1523 neonates 29020 patient days	Post implementation NICU-attributable clinical SA isolates -83 patients; 153 isolates MRSA – 11(7.2%) and MSSA 142 (92.8%) HAI – 43 Isolates of MSSA BSI – 14 (32.6%) among HAI MSSA positive clinical cultures (pre vs post) 106 vs. 36 Incidence rate: 3.62 vs 1.62 per 1000 days 31 MSSA infections (per NHSN criteria) vs 12 MSSA infections during the post-intervention period. Incidence rate of MSSA infections was 1.07 per 1000 patient-days vs. 0.55 per 1000 patient-days period (IRR = 0.51; 95% CI = 0.14, 1.82). The mean quarterly incidence rate of NICU attributable MRSA positive clinical cultures was 0.27 vs

				0.16 per 1000 patient-days (IRR = 0.60; 95% CI = 0.05, 7.77).
7	Lyles et al(7) 2015 Observational study Multicentric Chicago	After 2008, by law they were doing active surveillance Collected the data for next 5 years Compliance rates were 94%		Acquisition rates of MRSA – 4.8 vs 4.5 vs. 1.2 vs 5.6 vs 2.6(p value =0.57)
8	Annie Voskertchian et al 2018(8) Before and after study	MRSA and MSSA screening and colonization 39 months (47135 days)	Only MRSA screening and decolonization 24 months (29200 patient days)	Pre vs post NICU attributable cultures – 74 vs 68 43% reduction in clinical isolates IRR: 0.57, 95% CI: 0.40–0.80 Non-statistically significant reductions in the overall incidence rate of S. aureus BSIs (IRR: 0.50, 95% CI 0.18–1.34)
9	Wisgrill et al. 2017(9) Included only VLBW neonates Before and after study Retrospectiv	MSSA screening and decolonization Mupirocin and Ocetinidin solutions were used for decolonization 2011-13 14,062 patient days	No policy 2014-16 15,568 patient days	50% reduction of incidence rates per 1,000 patient-days of MSSA-attributable infections (1.63 [95% CI 1.12–2.31] vs. 0.83 [95% CI 0.47–1.35], p = 0.024) Incidence rates of sepsis (0.92 [0.54–1.45] and 0.52

	e analysis			[0.25–0.95]; p = 0.142) and Pneumonia (0.72 [0.39–1.20]) and 0.31 [0.11–0.68]; p = 0.08) per 1,000 patient-days declined over the study period.
10	Khoury et al 2005 Before and after study	Active surveillance for colonization Sites: Umbilicus, rectum and nares Healthcare workers also screened and treated. Out of 28 neonates, w 6 neonates were found to be positive for colonization. 6 out of 110 HCW were colonized.	No policy	HAI with MRSA – 3.92 to 0 per 1000 days

Question

Should Organism specific surveillance vs. No surveillance be used for reduce related BSI in NICU?	
Population:	reduce related BSI in NICU
Intervention:	Organism specific surveillance
Comparison:	No surveillance
Main outcomes:	BSI;
Setting:	**NICU**
Perspective:	
Background:	
Conflict of interests:	None

ASSESSMENT

Problem Is the problem a priority?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Hospital acquired infections is very important problem in our NICU settings. Incidence of sepsis in Indian scenario reported incidence upto 14.3% (95% CI 13·8–14·9) (DeNIS study). Among them culture proven sepsis is reported as 6.2% (5.8-6.6). Around two thirds of these infections occur at or after 72 hours of life. Many factors will influence the spread of HAIs. One of the important intervention is surveillance cultures. Routine surveillance of organisms seems no role according to recent CDC guidelines.	
Desirable Effects How substantial are the desirable anticipated effects?		
Judgement	Research evidence	Additional considerations
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Organism specific surveillance for MSSA and MRSA has shown benefits in reducing HAI (RR:0.58; 95% CI: 0.45-0.76) and clinical aquisition (colonization during hospital stay) (0.55; 0.43-0.76). It was not able to demonstrate any effects in reducing mortality and BSI rate. Studies didn't showed any increase in antibiotic resistance pattern due to treatment	

	of colonized infants with topical therapy.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
Judgement	Research evidence	Additional considerations
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	Organism specific surveillance for MSSA and MRSA has shown benefits in reducing HAI (RR:0.58; 95% CI: 0.45-0.76) and clinical aquisition (colonization during hospital stay) (0.55; 0.43-0.76). It was not able to demonstrate any effects in reducing mortality and BSI rate. Studies didn't showed any increase in antibiotic resistance pattern due to treatment of colonized infants with topical therapy.	
Certainty of evidence What is the overall certainty of the evidence of effects?		
Judgement	Research evidence	Additional considerations
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The evidence is based on pooling of few studies. The methodology and co-interventions described in the studies were different. All of them are observational studies (before and after type). Care pattern may have changed during the intervention periods which can influence the outcome.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
Judgement	Research evidence	Additional

		considerations
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	This metanalysis looked at studies for decreasing MSSA and MRSA related infections. It may not be major problem in tropical region who are more burdened with gram negative infections.	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Most of the studies have shown atleast decrease in the rate of HAI as shown in the forrest plot. However, the magnitude of effect is very less.	
Resources required How large are the resource requirements (costs)?		
Judgement	Research evidence	Additional considerations

○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Organism specific surveillance requires personnel, infrastructure changes in the form of isolation rooms and lab facilities. The surveillance results will guide better cohorting of patients, however it is associated with cost to account for additional for aseptic precautions. Two studies reported at the cost of surveillance and its benifits.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
Judgement	Research evidence	Additional considerations
○ Very low ● Low ○ Moderate ○ High ○ No included studies	In Krachmer study, overall cost of surveillance cultures during this outbreak was $27 589.73 and attributable excess cost of $17 422 for MRSA (as compared with MSSA) bacteraemia. To prevent 75 BSI and 4 deaths we need to spend $1 306 600. Other study by Kaushik et al. has showed that direct screening cost was $208 per patient. Since 28 neonates had to be screened to detect one colonization, $5,824 was estimated per detection. However, we couldn't find any Indian studies to look at the cost effectiveness.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
Judgement	Research evidence	Additional considerations

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	In Krachmer study, overall cost of surveillance cultures during this outbreak was $27 589.73 and attributable excess cost of $17 422 for MRSA (as compared with MSSA) bacteraemia. To prevent 75 BSI and 4 deaths we need to spend $1 306 600. Other study by Kaushik et al. has showed that direct screening cost was $208 per patient. Since 28 neonates had to be screened to detect one colonization, $5,824 was estimated per detection. However, we couldn't find any Indian studies to look at the cost effectiveness. We were not able to compare this in the pooled data due to methodological issues.	
Equity What would be the impact on health equity?		
Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	With organism specific surveillance, it has shown to reduce HAIs. Howver, these studies were conducted where the prevalence of colonozation is 20-40%. Indian studies are needed to look at the colonization rates and its impact.	
Acceptability Is the intervention acceptable to key stakeholders?		
Judgement	Research evidence	Additional considerations
○ No	Though it has shown moderate effect on	

● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	reduction of HAI and colonization, the cost occured for the same is very high. Surveillance requires lot of resources as mentioned above.The cost effective studies need to be conducted before finalizing the strategies.	
Feasibility Is the intervention feasible to implement?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	The intervention requires lot of resources howevrer it is easy to implement. Surveillance doesn't need new technologies.	

SUMMARY OF JUDGEMENTS:

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

	JUDGEMENT						
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

Conclusions

Recommendation

Organism specific surveillance for MSSA and MRSA has been shown to reduce HAI (Very Low quality- Weak recommendation) and Colonization during hospital stay (L ow quality evidence - weak recommendation). It didn't reduce related BSI rate (Very low quality evidence) and mortality (Low quality).

Justification

Overall justification

GRADE table below mentions the pooled data analysis for major outcomes.

Detailed justification

Desirable Effects

Organism specific surveillance for MSSA and MRSA has shown benefits in reducing HAI (RR:0.58; 95% CI: 0.45-0.76) and clinical acquisition (colonization during hospital stay) (0.55; 0.43-0.76). It was not able to demonstrate any effects in reducing mortality and BSI rate. Studies didn't show any increase in antibiotic resistance pattern due to treatment of colonized infants with topical therapy.

Cost effectiveness

As mentioned earlier, the cost involved seems very high for our settings and also number need to treat is very high.

Subgroup considerations

We couldn't do as only one study reported screening for VLBW infants alone.

Implementation considerations

Before going for routine organism specific surveillance, we need to first upgrade other aseptic precautions in NICU services. Once, sufficient resources and infrastructure available for cohorting then we can consider screening for these organisms.

Monitoring and evaluation

Organism specific surveillance requires very good monitoring and evaluation systems to look at the compliance rates of screening and decolonization programs efficacy.

Research priorities

More studies need to be done in Indian settings. The studies should aim at first looking at the colonization rates and magnitude of related HAI. Second priority will be look at the effectiveness of interventions. Newer methods of decolonization can also become a research priority.

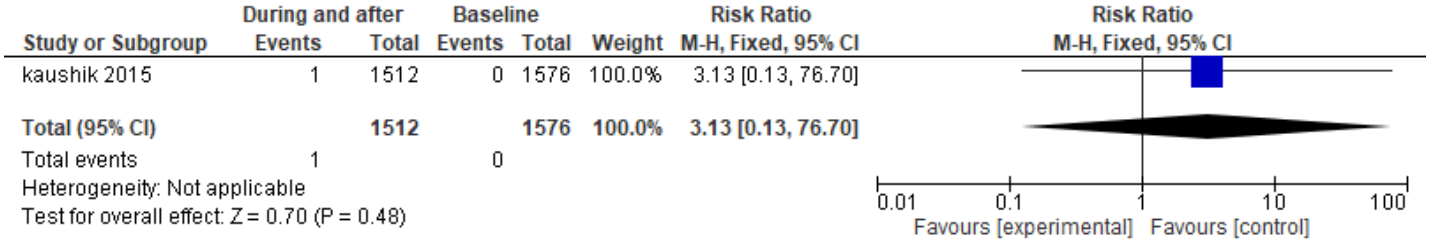
Author(s): Tejo Pratap, Srinivas Murki, Rajendra Prasad, Venkataseshan S, Avneet Kaur, Kamal Arora

Date: 2/10/19

Question: Hand Rub compared to Hand Wash in in neonates for prevention of infections

Setting: Neonatal units

Outcome 1



Question: Organism specific surveillance compared to No surveillance for reducing Mortality in NICU

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Organism specific surveillance	No surveillance	Relative (95% CI)	Absolute (95 % CI)		
New outcome												
1	observational studies	not serious	not serious	not serious	serious [a]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect dose response gradient [b]	1/1516 (0.1%)	0/1576 (0.0 %)	not estimable		⊕⊕◯◯ LOW	CRITICAL

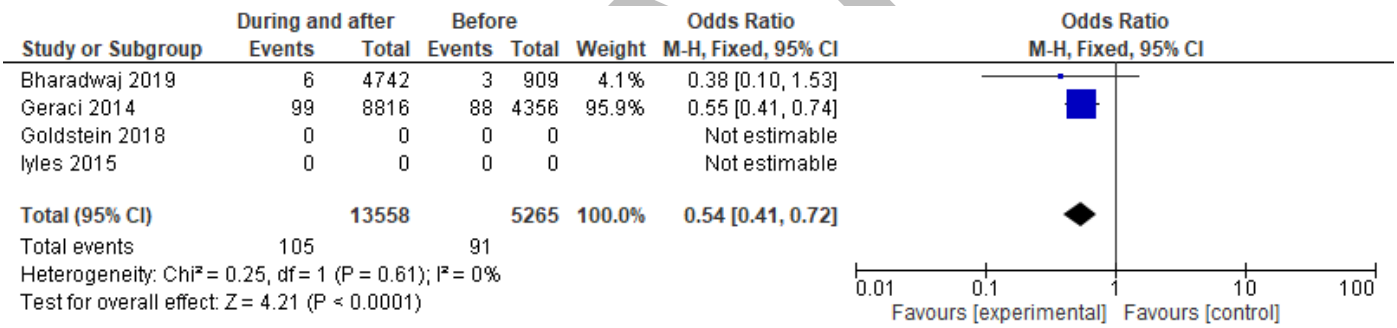
CI: Confidence interval

Explanations

a. NNT is very high

b. Only one study included

Outcome 2 Colonization



In Goldstein 2018 and Lyles 2015 studies, pre-intervention data was not available.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Organism specific surveillance	No surveillance	Relative (95% CI)	Absolute (95% CI)		
Colonization rates												
2	observational studies	serious [a]	serious [b]	serious [c]	not serious	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect dose response gradient [d]	105/13558 (0.8%)	91/5265 (1.7%)	**OR 0.54** (0.41 to 0.72)	**8 fewer per 1,000** (from 10 fewer to 5 fewer)	⊕⊕◯◯ LOW	IMPORTANT

.

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Both studies have not compared the profile of patients. Mean patient days were more during intervention periods in Geraci et al. study

b. Wide variation in RR intervals though heterogeneity is less.

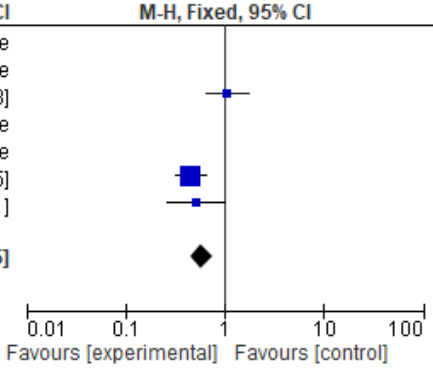
c. Both studies involved other QI strategies to decrease colonization.

d. Only 2 studies were included. Other strategies were also used simultaneously.

Outcome 3 HAI

Study or Subgroup	During and after Events	Total	Before Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Annie 2018	0	0	0	0		Not estimable
Bharadwaj 2019	0	4742	0	909		Not estimable
Geraci 2014	49	8816	23	4356	19.9%	1.05 [0.64, 1.73]
kaushik 2015	0	0	0	0		Not estimable
Khoury 2005	0	0	0	0		Not estimable
VO Poopola 2016	39	22045	114	29020	64.0%	0.45 [0.31, 0.65]
Wisgrill 2017	12	14062	26	15568	16.1%	0.51 [0.26, 1.01]
Total (95% CI)		**49665**		**49853**	**100.0%**	**0.58 [0.45, 0.75]**
Total events	100		163			

Heterogeneity: Chi² = 7.56, df = 2 (P = 0.02); I² = 74%
Test for overall effect: Z = 4.10 (P < 0.0001)



Risk of Bias
A B C D E F G

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

We were not able to pool the data of Khoury 2005 as they have expressed it in infections per number of patients. Crude data was not available for other studies as they expressed it as HAI per 1000 days.

Question: Organism specific surveillance compared to No surveillance for reducing HAI in NICU

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Organism specific surveillance	No surveillance	Relative (95% CI)	Absolute (95% CI)		
HAI												
4	observational studies	serious [a]	serious [b]	serious [c]	serious [d]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect dose response gradient [e]	100/49665 (0.2%)	163/49853 (0.3%)	**OR 0.58** (0.45 to 0.75)	**1 fewer per 1,000** (from 2 fewer to 1 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. In Wisgrill et al. study only VLBW neonates were included. Two studies were done as QI projects, others were pre and post intervention analysis. Difference in profile of patients were not mentioned in Bhardwaj et al, Geraci et al and Popola et al. study. No exclusion criteria were mentioned across studies.

b. Wide variation of RRs is seen. Overlapping CIs seen. I2 statistic – 74%

c. Wisgrill et al. included only VLBW and screened for MSSA also. Screening areas are different. Outcomes measures are direct only and similar.

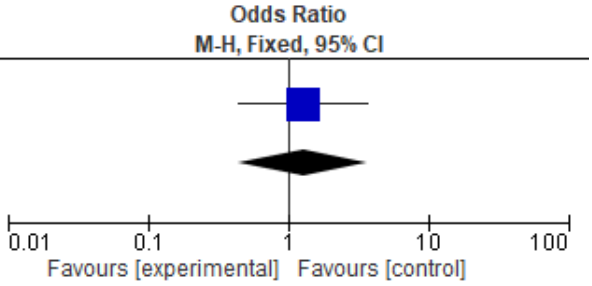
d. NNT is large.

e. Only 4 studies are included

Outcome 4 BSI

Study or Subgroup	during and after Events	Total	before Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Annie 2018	0	0	0	0		Not estimable
kaushik 2015	8	1576	6	1512	100.0%	1.28 [0.44, 3.70]
Total (95% CI)		**1576**		**1512**	**100.0%**	**1.28 [0.44, 3.70]**
Total events	8		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.65)



Question: Organism specific surveillance compared to No surveillance for reduce related BSI in NICU

Annie 2018 didn't provided crude date in the article and expressed it as BSI per 1000 days.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Organism specific surveillance	No surveillance	Relative (95% CI)	Absolute (95% CI)		
BSI												
1	observational studies	not serious	not serious	serious [a]	serious [b]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect dose response gradient [c]	8/1576 (0.5%)	6/1512 (0.4%)	**OR 1.28** (0.44 to 3.70)	**1 more per 1,000** (from 2 fewer to 11 more)	⊕◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. They have not provide the patient days. They only provided number of patients during the period.

b. Wide RR interval.

c. Only 1 study was included.

Grade assessment Criteria	Bharadwaj	Geraci	Poopola	Wisgrill	Kaushik	
Risk of bias **1. Failure to develop and apply appropriate inclusion criteria** **2. Flawed measurement of exposure/ outcome (differential measurement or surveillance in exposed and unexposed groups)** **3. Failure to adequately control confounding** **4. Incomplete or inadequate (short) follow-up**	Recent article Multiple interventions Prospective Included all neonates for screening Follow up is good Profile is not mentioned	Prospective study Included all neonates Comparison of profile is not mentioned. There was overcrowding as mentioned in the article. Mean patient days were more during intervention periods.	Pre and post study Targeted both MSSA and MRSA Comparative profile is not mentioned.	Only VLBW neonates are considered. No definite exclusion criteria. Multiple births were more in preinterventio n period. PVC and patient days are more in the post-intervention period. Both are not adjusted.	Before and after study. Methodology described properly.	
Inconsistency **1. Wide variance in RR/OR across studies (direction of effect not a criterion)** **2. Minimal or no overlap of Cis** **3. I^2 statistic (dependent on sample size): <40%- low, 30-60%- moderate, 50-90%- substantial, 75-100%- considerable** **4. τ^2 (independent of sample size)**	HAI: Wide variation of RRs is seen. Overlapping CIS seen. I^2 statistic – 74% Colonization I^2 statistic – zero Wide variation of RRs				NA	
Indirectness **1. Differences in population (applicability)** **2. Differences in intervention (applicability)- delivered differently in different settings** **3. Differences in outcome measures (surrogate outcomes)- outcomes**	HAI Wisgrill et al. included only VLBW and screened for MSSA also. Screening areas are different. Outcomes measures are direct only and similar. Colonization Populations were not mentioned in Geraci group. Overcrowding was mentioned.				NA	

measured at different time points/ surrogate instead of patient-important outcomes **4. Indirect comparisons**			
Imprecision **1. CI crosses the clinical decision threshold (e.g., NNT of 1 in 200/0.5% ARR for a low cost and safe intervention; NNT of 1 in 20 or 5% ARR for an intervention with serious risks; 1 day for hospital stay, a continuous outcome)** **2. Not optimal information size (the total number of patients included in a systematic review is less than the number of patients generated by a conventional sample size calculation for a single adequately powered trial. Use RRR of 20-30%. Calculator link-** http://www.stat.ubc.ca/rollin/stats/ssize/b2.html**)**	HAI Will reduce by 1 in 1000 patient days Colonization NNT: 1 in 100	Wide RR	
Publication bias **1. Asymmetry of funnel plots (only if >10 studies included)** **2. Evidence is limited to a small number of small trials, esp if many of these show benefits** **3. Trim and fill method**	HAI – 4 studies Colonization: 2 studies		

Q7: In neonatal units, does routine environmental surveillance as compared to no surveillance decrease HAIs?

Objective

To evaluate whether routine environmental surveillance as compared to no surveillance decrease HAI in neonatal units?

Methods

Participants

Infants admitted to NICU for more than 48 hours

Intervention: Routine environmental surveillance

Control: No environmental surveillance

Outcome

The primary outcome was the number of HAIs per 1000 central line or patient days.

A HAI is an infection (that occurs without an apparent infection at admission) that develops in a patient that developed after 48 hrs of admission into health facility. Healthcare-associated infections (HAIs) include central line-associated bloodstream infections, catheter-associated urinary tract infections, and ventilator-associated pneumonia. Infections may also occur at surgery sites, known as surgical site infections.

Definition of interventions

Environmental surveillance (ES)

Culturing of the air and environmental surfaces (e.g., floors, walls, water and table tops)

Routine ES policy

Random or untargeted/ undirected ES done to check microbial colonization in health care facilities periodically.

No ES policy

Contrary to the policy mentioned above, if ES is done only in specific situations like outbreak or to target a drug resistant pathogen, those policies are included in this category.

Surveillance include air, water and surface samplings. Water samples can be collected from taps running at wash basins, water used in humidifiers and for drug dilutions. Surface samplings will be done from surrounding environment of the neonate like equipment.

Results

Literature search:

We conducted a comprehensive search with following terms in the month of August:

Environmental surveillance; Healthcare associated infection; Neonatal intensive care unit; environmental monitoring; environmental; Environmental sampling; Neonate; Intensive care units;

Even after broadening the search terms, we could not find any eligible articles for the inclusion. Many of the articles targeted environmental sampling during outbreaks and eliminating some organisms. Some articles have focused on the correlation between environmental pathogens and organism grown in the admitted neonates.

Search strategy widened to look for adult and pediatric intensive care units also. However, we couldn't find any eligible articles.

We looked at the existing guidelines to answer the research question. We adopted to the following recommendations after looking Centre for Disease Control (CDC) and Healthcare Infection Control Practices Advisory Committee (HICPAC) guidelines. These are published in 2003 and updated in 2017.

Recommendations

- According to the existing guidelines and research, routine environmental surveillance is not superior to the routine disinfection control programs.

S.No	Recommendation	Category
1	Do not conduct random, undirected microbiologic sampling of air, water, and environmental surfaces in health-care facilities	I B
2	When indicated, conduct microbiologic sampling as part of an epidemiologic investigation or during assessment of hazardous environmental conditions to detect contamination and verify abatement of a hazard.	I B
3	Limit microbiologic sampling for quality assurance purposes to • biological monitoring of sterilization processes;	I B

	• monthly cultures of water and dialysate in hemodialysis units; and • short-term evaluation of the impact of infection-control measures or changes in infection- control protocols.	

IB – Strongly recommended for implementation and supported by certain experimental, clinical, or epidemiologic studies and a strong theoretical rationale.

Microbiologic sampling of air, water, and inanimate surfaces (i.e., environmental sampling) is an expensive and time-consuming process that is complicated by many variables in protocol, analysis, and interpretation. It is therefore indicated for only four situations.

1. Outbreak of an organism

To support an investigation of an outbreak of disease or infections when environmental reservoirs or fomites are implicated epidemiologically in disease transmission. It is important that such culturing be supported by epidemiologic data. Environmental sampling, as with all laboratory testing, should not be conducted if there is no plan for interpreting and acting on the results obtained. Linking microorganisms from environmental samples with clinical isolates by molecular epidemiology is crucial whenever it is possible to do so.

2. Research setting

Well-designed and controlled experimental methods and approaches can provide new information about the spread of healthcare associated diseases. A classic example is the study of environmental microbial contamination that compared health-care associated infection rates in an old hospital and a new facility before and shortly after occupancy.

3. Potentially hazardous environmental condition

Confirm the presence of a hazardous chemical or biological agent and validate the successful abatement of the hazard. This type of sampling can be used to:

- Detect bioaerosols released from the operation of health-care equipment (e.g., an ultrasonic cleaner) and determine the success of repairs in containing the hazard,
- Detect the release of an agent of bioterrorism in an indoor environmental setting and determine its successful removal or inactivation, and
- Sample for industrial hygiene or safety purposes (e.g., monitoring a "sick building").

4. Quality assurance

To evaluate the effects of a change in infection-control practice or to ensure that equipment or systems perform according to specifications and expected outcomes. Any sampling for quality-assurance purposes must follow sound sampling protocols and address confounding factors using properly selected controls. Results from a single environmental sample are difficult to interpret in the absence of a frame of reference or perspective. Evaluations of a change in infection-control practice assume that the effect will be measured over a finite period, usually of short duration. Conducting quality-assurance sampling on an

extended basis, especially in the absence of an adverse outcome, is usually unjustified. A possible exception might be the use of air sampling during major construction periods to qualitatively detect breaks in environmental infection-control measures.

Q8: Among pregnant women with leaking membranes and are at risk of preterm birth, does administration of antibiotics versus no antibiotics/placebo reduce the risk of neonatal infections and other major outcomes?

Objectives

To assess whether administering antibiotics to pregnant women with preterm premature rupture of membranes in comparison to not administering anything or administering placebo

a) would reduce the risk of neonatal infection including pneumonia
b) would reduce the risk of perinatal death/death before discharge from hospital
c) would reduce the risk of major central nervous system abnormalities in ultrasound before discharge
d) would reduce the long-term Neurodevelopmental outcome (18-24 months)
e) would reduce the risk of necrotizing enterocolitis
f) would reduce the risk of need for oxygen by 36 weeks PMA
g) would reduce the risk of low birth weight (weight <2500 grams)
h) would reduce the risk of need for neonatal intensive care admission
i) would reduce the risk of neonatal respiratory distress syndrome
j) would reduce the risk of neonatal encephalopathy
k) would reduce the risk of serious childhood disability at 5-7 years of age

Priority question broken in a PICO format

Participants: pregnant women of <37 weeks' gestation and with rupture of membranes and are at risk of preterm birth

Intervention: Antibiotics (intravenous or intramuscular) of any classification or group

Comparison: No antibiotics or a placebo agent

Outcomes and their definitions:

CRITICAL- Perinatal death/death before discharge from hospital, neonatal infection including pneumonia, major central nervous system abnormalities in ultrasound before discharge, long-term Neurodevelopmental outcome (18-24 months)

IMPORTANT- necrotizing enterocolitis, need for oxygen by 36 weeks PMA, need for neonatal intensive care admission

LESS IMPORTANT- low birth weight (weight <2500 grams), neonatal respiratory distress syndrome, neonatal encephalopathy, serious childhood disability at 5-7 years of age

Outcomes	**Definition**
Perinatal death/death before discharge from hospital	Death of a fetus after completion of 28 weeks' gestation plus neonatal mortality till 28 days of life or till discharge from hospital
Neonatal infection including pneumonia	Neonatal infections (pneumonia/ sepsis/ meningitis/etc.) developed any time after birth
Major central nervous system abnormalities in ultrasound before discharge	USG proven intraventricular hemorrhage of grade 2 and above, periventricular cystic leukomalacia of grade 2 and above, ventriculomegaly due to post-meningitis or post-hemorrhagic

Long-term Neurodevelopmental outcome (18-24 months)	Abnormal neuro-developmental outcome at 18-24 months of age as assessed using a standard neuro and developmental assessment tool
Necrotizing enterocolitis	Defined as stage 2 and above using the modified Bells staging system
Need for oxygen by 36 weeks PMA	Defined based on the NIH definition for BPD
Need for neonatal intensive care admission	Need for admission to the NICU
Low birth weight (weight <2500 grams)	Birth weight <2500 grams
Neonatal respiratory distress syndrome	Respiratory distress requiring respiratory support with onset within 6 hours of life with or without radiological evidence of RDS
Neonatal encephalopathy	Abnormal neurological status at birth defined based on standard neurological scoring system such as Levene's staging
Serious childhood disability at 5-7 years of age	Abnormal neuro-developmental outcome at 5-7 years of age as assessed using a standard neuro and developmental and intelligence assessment tool

Methods & Results

We searched PubMed using the search strategy "fetal membranes, premature rupture"[MeSH Terms] AND "anti-bacterial agents"[MeSH Terms] AND "infant, newborn"[MeSH Terms] AND "sepsis"[MeSH Terms]. Apart from this search, we also used keywords to search PubMed with "newborn/neonate, antibiotics, sepsis/infection, rupture of membranes" as keywords with appropriate Boolean

operators. We did a similar search using the above key words in the Cochrane Central and identified one Cochrane systematic review and meta-analysis of randomized trials (Pregnancy and Childbirth group) that examined the effect of administering antibiotics to pregnant women with leaking membranes and are at risk of preterm birth in comparison to no antibiotics or placebo (Kenyon S, Boulvain M, Neilson JP. Antibiotics for preterm rupture of membranes. Cochrane Database Syst Rev. 2013;(12):CD001058). It had 22 randomized trials included in the review and was last amended on 17th December 2013. Post-Cochrane, there has been no new intervention trials, even though we could identify few observational studies. Based on the above systematic review, the World Health Organization (WHO) has published a guideline titled "WHO Recommendations on interventions to improve preterm birth outcomes: evidence base" (ISBN 978 92 4 150898 8). A lot many information has been extracted from the WHO guidelines as a base document

Results of few key outcomes:

The GRADE table (see below) enlists the effect size for the available key outcomes for the comparison of interventions

1. Perinatal death / death before discharge: A total of 12 randomized trials addressed this outcome and the evidence has Moderate certainty. Serious risk of bias was observed for imprecision. Even though there seemed to be trend in reduction of perinatal death, the effect was not statistically significant.
2. Neonatal infections including pneumonia: A total of 12 randomized trials addressed this outcome. There was a 33%reduction in the risk of

neonatal infections including pneumonia with 54 fewer cases of the outcome for every 1000 pregnant women treated with antibiotics.

3. Major cerebral abnormalities on ultrasound before discharge: A total of 12 randomized trials addressed this outcome. There was a 19% reduction in the risk of this outcome which was statistically significant. There were 18 fewer neonates with major cerebral USG abnormalities for every 1000 pregnant women treated with antibiotics
4. None of the critical rated neonatal outcomes were observed to have a significant impact on administering antibiotics to pregnant women

Table 1: GRADE table key outcomes

Author(s): Venkataseshan Sundaram, Srinivas Murki, Rajendra Prasad, Avneet kaur, Manoj Malviya, Kamal Arora, Tejo Pratap Oleti

Date: 27/10/2019

Question: Antibiotics compared to No antibiotics or placebo for pregnant women at risk of preterm birth and with ruptured membranes

Setting: Hospital

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	No antibiotics or placebo	Relative (95% CI)	Absolute (95% CI)		
1. Perinatal death/death before discharge - Any antibiotic versus placebo												
12	randomised trials	not serious	not serious	not serious	serious [a]	none	276/4315 (6.4%)	138/1986 (6.9%)	**RR 0.93** (0.76 to 1.14)	**5 fewer per 1,000** (from 17 fewer to 10 more)	⊕⊕⊕◯ MODERATE	CRITICAL
2. Neonatal infection including pneumonia - Any antibiotic versus placebo												
12	randomised trials	not serious	not serious	not serious	not serious	none	85/823 (10.3%)	141/857 (16.5%)	**RR 0.67** (0.52 to 0.85)	**54 fewer per 1,000** (from 79 fewer to 25 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

3. Neonatal necrotizing enterocolitis - Any antibiotic versus placebo

11	randomised trials	not serious	not serious	not serious	serious [a]	none	100/4273 (2.3%)	58/1956 (3.0%)	**RR 1.09** (0.65 to 1.83)	**3 more per 1,000** (from 10 fewer to 25 more)	⊕⊕⊕◯ MODERATE	CRITICAL

4. Major cerebral abnormality on ultrasound before discharge - Any antibiotic versus placebo

12	randomised trials	not serious	not serious	not serious	not serious	none	240/4303 (5.6%)	184/1986 (9.3%)	**RR 0.81** (0.68 to 0.98)	**18 fewer per 1,000** (from 30 fewer to 2 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT

5. Birth before 37 weeks' gestation

3	randomised trials	not serious	not serious	not serious	not serious	none	3104/3642 (85.2%)	1102/1289 (85.5%)	**RR 1.00** (0.98 to 1.03)	**0 fewer per 1,000** (from 17 fewer to 26 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

6. Chorioamnionitis

11	randomised trials	not serious	not serious	not serious	not serious	none	126/767 (16.4%)	196/792 (24.7%)	**RR 0.66** (0.46 to 0.96)	**84 fewer per 1,000** (from 134 fewer to 10 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT

Birthweight

12	randomised trials	not serious	not serious	not serious	not serious	none	4355	2019	-	MD **53.83 higher** (7.06 higher to 100.6 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT

Birthweight < 2500 g

2	randomised trials	not serious	not serious	not serious	not serious	none	2605/3614 (72.1%)	911/1262 (72.2%)	**RR 1.00** (0.96 to 1.04)	**0 fewer per 1,000** (from 29 fewer to 29 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

Neonatal intensive care

4	randomised trials	not serious	serious [c]	not serious	not serious	none	2583/3687 (70.1%)	975/1336 (73.0%)	**RR 0.98** (0.84 to 1.13)	**15 fewer per 1,000** (from 117 fewer to 95 more)	⊕⊕⊕◯ MODERATE	CRITICAL

Days in neonatal intensive care unit

3	randomised trials	serious [d]	not serious	not serious	serious [e]	none	110	115	-	MD **5.05 lower** (9.77 lower to 0.33 lower)	⊕⊕◯◯ LOW	IMPORTANT

Positive neonatal blood culture

3	randomised trials	not serious	not serious	not serious	not serious	none	234/3654 (6.4%)	104/1307 (8.0%)	**RR 0.79** (0.63 to 0.99)	**17 fewer per 1,000** (from 29 fewer to 1 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

Neonatal respiratory distress syndrome

12	randomized trials	not serious	not serious	not serious	not serious	none	965/4303 (22.4%)	551/1984 (27.8%)	**RR 0.95** (0.83 to 1.09)	**14 fewer per 1,000** (from 47 fewer to 25 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Neonatal encephalopathy

1	randomised trials	serious [b]	not serious	not serious	very serious [f]	none	0/30 (0.0%)	0/30 (0.0%)	not estimable		⊕◯◯◯ VERY LOW	IMPORTANT

Serious childhood disability at 7 years

1	randomised trials	not serious	not serious	not serious	not serious	none	938/2375 (39.5%)	311/796 (39.1%)	**RR 1.01** (0.91 to 1.12)	**4 more per 1,000** (from 35 fewer to 47 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

Perinatal death/death before discharge - Antibiotics versus no antibiotics (all studies)

18	randomised trials	not serious	not serious	not serious	serious [a]	none	299/4604 (6.5%)	172/2268 (7.6%)	**RR 0.89** (0.74 to 1.08)	**8 fewer per 1,000** (from 20 fewer to 6 more)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Wide confidence intervals crossing the line of no-effect

b. Single study with design limitations

c. Statistical heterogeneity (I2 was > 60%)

d. half the weightage came from a single study which has design limitations

e. Estimate based on small sample size

f. No events occurred / documented

QUESTION

Should Antibiotics vs. No antibiotics or placebo be used for pregnant women at risk of preterm birth and with ruptured membranes?	
POPULATION:	pregnant women at risk of preterm birth and with ruptured membranes
INTERVENTION:	Antibiotics
COMPARISON:	No antibiotics or placebo
MAIN OUTCOMES:	Perinatal death/death before discharge - Any antibiotic versus placebo; Neonatal infection including pneumonia - Any antibiotic versus placebo; Neonatal necrotising enterocolitis - Any antibiotic versus placebo; Oxygen treatment > 36 weeks' postconceptual age - Any antibiotic versus placebo; Major cerebral abnormality on ultrasound before discharge - Any antibiotic versus placebo; Birth before 37 weeks' gestation; Chorioamnionitis; Birthweight; Birthweight < 2500 g; Neonatal intensive care; Days in neonatal intensive care unit; Positive neonatal blood culture; Neonatal respiratory distress syndrome; Neonatal encephalopathy; Serious childhood disability at 7 years; Perinatal death/death before discharge - Antibiotics versus no antibiotics (all studies);
SETTING:	Hospital
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	A large proportion of premature births result from spontaneous preterm labour and from preterm rupture of the membranes (PROM). Once the membranes have ruptured prematurely, 50% of women will go into labour within 24 to 48 hours and 70% to 90% within seven days (Dale 1989). Children born preterm are at increased risk of major disabilities, such as cerebral palsy, with the risk increasing with decreasing gestation at birth (Costeloe 2012; Marlow 2005). Apart from disabilities, risk of neonatal infections is high in babies born to mothers with PROM. Infection appears to have an important role, either as a cause or as a consequence of PROM. There is increasing evidence that, in addition to preterm birth, perinatal infection is an independent antecedent of other disability, particularly cerebral palsy and chronic lung disease (Dammann 2005; Romero 2007). The prevention of preterm birth and reduction of associated disability are therefore important health priorities.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ● Large ○ Varies	Desirable anticipated effects are reduction in rates of neonatal infections including pneumonia, major cerebral abnormalities in postnatal ultrasound, perinatal death and long-term neurodevelopmental outcome. A simple intervention such as antibiotics to	

○ Don't know	pregnant women with PROM that can reduce the risk of the above problems would be substantial Cost of antibiotics, adequate and consistent supply of drugs, correct selection of choice of drugs and possible masking of neonatal infections due to intrapartum antibiotics would be undesirable effects	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	Desirable anticipated effects are reduction in rates of neonatal infections including pneumonia, major cerebral abnormalities in postnatal ultrasound, perinatal death and long-term neurodevelopmental outcome. A simple intervention such as antibiotics to pregnant women with PROM that can reduce the risk of the above problems would be substantial Cost of antibiotics, adequate and consistent supply of drugs, correct selection of choice of drugs and possible masking of neonatal infections due to intrapartum antibiotics would be undesirable effects	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Overall certainty of evidence of effects is high for neonatal infections including pneumonia whereas it was moderate for major cerebral abnormalities in postnatal ultrasound and positive neonatal blood culture	

Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The available evidence from systematic reviews and individual observational studies seem to suggest that many obstetricians believe that intrapartum antibiotics in pregnant mother would help in preventing few important maternal and neonatal adverse effects. Even though there is not direct indication about how people value the main outcomes, reducing the risk of neonatal infections including pneumonia seem to carry a lot of value.	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	The only undesirable effect stated in individual controlled trials is the possible masking of neonatal infection due to the intrapartum antibiotics. However, there is no evidence to prove this statement. We believe the balance favors the intervention	

Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	No study has analyzed the cost effectiveness or cost benefit aspect of administering antibiotics.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies		No evidence available to comment about the resource requirements
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the	No study has included cost-effectiveness as part of their analysis	

intervention ○ Favors the intervention ○ Varies ● No included studies		
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Data from the controlled trials have mainly come from high income countries such as USA, UK and Germany. More than 60% of the recruited pregnant women were from a single UK trial. Hence, direct applicability to low- and middle-income countries is less	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Even though no separate cost-effectiveness and cost-benefit analysis was done for antibiotics usage in pregnant women, the antibiotics studied and were found effective are cheap, available easily and can be made available as part of routine government supply No serious adverse effects were reported. Hence, we believe this intervention for the reported outcomes would be acceptable to stakeholders	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No separate feasibility studies could be identified. However, none of the studies reported difficulties in implementation	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the	Does not favor either	Probably favors the	**Favors the**	Varies	Don't know

	JUDGEMENT						
		comparison	the intervention or the comparison	intervention	**intervention**		
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

Antibiotic administration while a pregnant mother is in labor with leaking membranes is recommended

Justification

Overall justification

Administering antibiotics has been reported across clinical trials to convincingly reduce the risk of neonatal infection including pneumonia.

Moreover, it was also observed to reduce the risk of blood culture positive sepsis and major cerebral abnormalities in ultrasonography

Detailed justification

Desirable Effects

Reduction in neonatal infection including pneumonia

Certainty of evidence

Certain

Feasibility

Feasible in an Indian context

Subgroup considerations

None of the available studies have been investigated in the Indian subcontinent. However, with the available evidence, we believe that administering antibiotics might benefit more due to the higher baseline risk of infections in neonates.

Implementation considerations

A uniform policy across the country, explicit indications and standard operating procedure and procurement, supply and cost considerations of antibiotics need to be addressed

Monitoring and evaluation

Audit for neonatal infections, maternal chorioamnionitis, prevention of preterm birth, need for intensive care admission and long-term neurodevelopmental outcomes is required to be built into the system

Research priorities

Intervention trial comparing intrapartum antibiotics versus none and versus placebo and head to head comparison of various group of antibiotics are required in a multicentric fashion covering various regions with varying obstetric and neonatal practices is required