# WHO Guideline for Management of Possible Serious Bacterial Infection (PSBI) in neonates and young infants where referral is not feasible

**Department of Maternal, Newborn, Child & Adolescent Health** 



## **Newborn Infections**

#### **PROBLEM:**

- Newborn infections cause a quarter of neonatal deaths
- Recommended treatment can be given only in hospitals
- Hospitalization is not an option for many sick young infants in LMICs

#### How common is Possible Serious Bacterial Infection (PSBI)?

2012 systematic review and meta-analysis reported

- Estimated 6.9 million cases of PSBI occurred
  - 3.4 million cases in South Asia
  - 2.6 million in sub-Saharan Africa
  - 0.8 million in Latin America
- PSBI case fatality ratio (CFR) was 9.8%
- PSBI incidence risk was 7.6% (95% CI 6-1-9.2)



# **Referral is not accepted for PSBI: 68-98%**

- Hospital treatment not accessible at all or in time in resource limited settings
- In some settings majority of families <u>do not</u> accept referral

| <ul> <li>Bhandari et al Lancet India 1996</li> </ul>           | 76%        |
|--|------------|
| <ul> <li>Bang et al India, Lancet 1999</li> </ul>              | <b>98%</b> |
| <ul> <li>Baqui et al Bangladesh Lancet 2008</li> </ul>         | <b>68%</b> |
| <ul> <li>Zaidi et al Pakistan PIDJ 2012</li> </ul>             | 78%        |
| <ul> <li>Baqui et al SATT Bangladesh Lancet GH 2014</li> </ul> | 84%        |
| <ul> <li>DR Congo, AFRINEST, Lancet 2014</li> </ul>            | 71%        |
| <ul> <li>Kenya AFRINEST, Lancet 2014</li> </ul>                | 89%        |
| <ul> <li>Nigeria AFRINEST, Lancet 2014</li> </ul>              | 78%        |



# **PSBI Study**

#### AIM:

 To find deliverable and effective treatment for newborns with signs of severe infection where referral is not possible



## **Research in programme settings**





## **Participants**

#### Young infants with clinical signs of severe infection whose parents do not or cannot accept hospital referral

#### **INCLUSION SIGNS:**

- Stopped feeding well
- Movement only when stimulated
- Severe chest in-drawing
- Temperature ≥38.0°C
- Temperature <35.5°C</p>

#### **EXCLUSION SIGNS:**

- Unconscious
- Convulsions
- Apnoea
- Unable to feed
- Unable to cry
- Persistent vomiting
- Major bleeding
- Cyanosis
- Bulging fontanel
- Weight <1500 grams
- Major congenital malformation
- Surgical conditions requiring hospitalization

## Fast breathing only: Intervention and Control

#### **Control arm (reference treatment)**

<u>**A**</u>: IM gentamicin <u>and</u> procaine penicillin OD for 7 days

14 injections

#### Simpler regimens

**E**: Oral amoxicillin BD for 7 days

No injections

#### **Outpatient treatment by health workers** (CHEWs, nurses, physicians)

Procaine penicillin 50,000 units/kg once daily IM; gentamicin 4.0-7.5 mg/kg/day once daily IM; oral amoxicillin suspension 75-100 mg/kg/day

## Severe Clinical infection: Intervention and Control

#### **Control arm (reference treatment)**

<u>**A**</u>: IM gentamicin <u>and</u> procaine penicillin OD for 7 days

**14 injections** 

#### **Simpler regimens**

**B**: IM gentamicin OD <u>and</u> oral amoxicillin BD for 7 days

7 injections

C: IM gentamicin OD <u>and</u> procaine penicillin OD for 2 days, thereafter oral amoxicillin BD for 5 days **4 injections** 

D: IM gentamicin OD <u>and</u> oral amoxicillin BD for 2 days, thereafter oral amoxicillin BD for 5 days
 2 injections

**Outpatient treatment by health workers** (CHEWs, nurses, physicians)

Procaine penicillin 50,000 units/kg once daily IM; gentamicin 4.0-7.5 mg/kg/day once daily IM; oral amoxicillin suspension 75-100 mg/kg/day

## <u>Outcomes</u>

**Primary outcome:** Treatment failure within 7 days of randomization

- Death or severe adverse event due to study antibiotics
- <u>Clinical deterioration</u>: emergence of any sign of critical illness, a (new) sign of severe infection, hospitalization
- Persistence: no improvement by day 4, not fully recovered by day 8

#### **Secondary outcomes**

- Death within 2 weeks after enrolment
- Relapse during the second week

Those who failed treatment were given ceftriaxone injections for 7 days

## **Study Sites**

|                            | DRC                  | Kenya               | Nigeria                    | Banglades<br>h         | Pakistan |
|----------------------------|----------------------|---------------------|----------------------------|------------------------|----------|
| Site                       | Equateur<br>Province | Western<br>province | Ibadan, Ile-<br>Ife, Zaria | 5 hospitals,<br>Sylhet | Karachi  |
| Study<br>population        | 400,000              | 400,000             | 700,000                    | -                      | 350,000  |
| Births/year                | 17,000               | 13,000              | 20,000                     | -                      | 15,000   |
| Infants with<br>PSBI /year | 2000                 | 1500                | 2500                       | -                      | 2000     |

Multi-country, multi-centre study in Africa, two additional studies in Asia: large sample size, high generalizability

# **AFRINEST - Fast breathing results**

# **Study flow: fast breathing**



# **Baseline characteristics of enrolled infants**

|                            | Penicillin and        | Oral amoxicillin for 7 |
|----------------------------|-----------------------|------------------------|
|                            | Gentamicin for 7 days | days [Arm E]           |
|                            | [Arm A]               |                        |
|                            | N= 1170               | N= 1163                |
| Age < 7 days               | 441 (37.7)            | 441 (37.9)             |
| Male                       | 631 (53.9)            | 644 (55.4)             |
| Mother <20 years           | 128 (11)              | 137 (11.8)             |
| Home birth                 | 519 (44.4)            | 507 (43.6)             |
| Mother not been to school  | 191 (16.3)            | 200 (17.1)             |
| Indoor cooking, solid fuel | 521 (44.5)            | 508 (43.7)             |
| Respiratory rate 60-69     | 446 (38.1)            | 446 (38.3)             |
| 70-79                      | 358 (30.6)            | 400 (34.4)             |
| <u>&gt;</u> 80             | 366 (31.3)            | 317 (27.2)             |

## **Oral Amoxicillin is Equivalent to Reference Treatment**

|   | Gentamicin &<br>Procaine pen<br>inj. | Oral<br>Amoxicilli<br>n | Risk difference<br>(95% CI) |
|---|--------------------------------------|-------------------------|-----------------------------|
|   | 1063                                 | 1145                    | (oral – injections)         |
| Treatment failure during 1 <sup>st</sup><br>week                  | 234 (21%)                            | 221 (19%)               | -3% (-6%, 1%)               |
| Individual Signs of failure                                       |                                      |                         |                             |
| Death   | 4 (0.4%)                             | 2 (0.3%)                |                             |
| Clinical deterioration  | 21 (2%)                              | 20 (2%)                 |                             |
| <i>Persistence of FB on day 4 or reappearance between day 5-8</i> | 209 (20%)                            | 199 (17%)               |                             |
| Severe adverse events   | 0                                    | 0                       |                             |
| Death during 2 weeks f/up   | 4                                    | 4                       | 0% (-0.5%, 0.5%)            |
| Relapse during 2 <sup>nd</sup> week                               | 18 (2%)                              | 22 (2%)                 | 0.2% (-1%, 2%)              |

# AFRINEST - Clinical severe infection results

## **Study flow: clinical severe infection**



# **Baseline characteristics of enrolled infants**

|                            | Penicillin and<br>Gentamicin for<br>7 days | Oral amox<br>and<br>Gentamicin<br>for 7 days | Penicillin and<br>gentamicin for<br>2 days, then<br>oral amox for 5 | Gentamicin<br>and oral amox<br>for 2 days, then<br>oral amox for 5 |
|----------------------------|--|--|---|--|
|                            | [Arm A]                                    | [Arm B]                                      | (Arm C]   | (Arm D)  |
|                            | N= 894                                     | N= 884                                       | N= 896  | N=890  |
| Age < 7 days               | 293 (32.8)                                 | 279 (31.6)                                   | 300 (33.5)  | 288 (32.4)   |
| Male                       | 486 (54.4)                                 | 463 (52.4)                                   | 454 (50.7)  | 498 (56.0)   |
| WAZ < -2                   | 160 (17.9)                                 | 137 (15.5)                                   | 160 (17.9)  | 154 (17.3)   |
| Mother <20 years           | 107 (12.0)                                 | 101 (11.4)                                   | 115 (12.8)  | 117 (13.2)   |
| Home birth                 | 343 (38.4)                                 | 356 (40.3)                                   | 363 (40.5)  | 371 (41.7)   |
| At least one ANC visit     | 850 (95.1)                                 | 834 (94.3)                                   | 845 (94.3)  | 842 (94.6)   |
| Birth order ≥4             | 319 (35.7)                                 | 339 (38.4)                                   | 337 (37.6)  | 347 (38.9)   |
| Mother not been to school  | 155 (17.3)                                 | 161 (18.2)                                   | 158 (17.6)  | 151 (17.0)   |
| Indoor cooking, solid fuel | 392 (43.6)                                 | 381 (42.7)                                   | 381(42.2)   | 380 (42.3)   |

# **Illness characteristics of enrolled infants**

|                                | Penicillin and<br>Gentamicin for<br>7 days | Oral amox<br>and<br>Gentamicin<br>for 7 days | Penicillin and<br>gentamicin for<br>2 days, then<br>oral amox for 5<br>days | Gentamicin<br>and oral amox<br>for 2 days, then<br>oral amox for 5<br>days |
|--------------------------------|--|--|---|--|
|                                | N= 894                                     | N= 884                                       | N= 896  | N=890  |
| Severe chest indrawing         | 392 (43.9)                                 | 384 (43.4)                                   | 393 (43.9)  | 384 (43.2)   |
| Temperature <35.5              | 40 (4.5)                                   | 44 (5.0)                                     | 58 (6.5)  | 49 (5.5)   |
| Temperature <u>&gt;</u> 38.0°C | 425 (47.6)                                 | 411 (46.5)                                   | 395 (44.1)  | 417 (46.9)   |
| Stopped feeding well           | 142 (15.9)                                 | 130 (14.7)                                   | 147 (16.4)  | 159 (17.9)   |
| Movement only on stimulation   | 21 (2.4)                                   | 33 (3.7)                                     | 22 (2.5)  | 23 (2.6)   |
| ≥1 sign of severe illness      | 113 (12.6)                                 | 108 (12.3)                                   | 107 (11.9)  | 124 (13.9)   |
| Received all treatment doses   | 827 (92.5)                                 | 835 (94.5)                                   | 868 (96.9)  | 863 (97.0)   |

### Simplified Regimens are Equivalent to Reference Treatment

|   | Gentamicin<br>& Pro. Pen<br>inj 14<br>injections | Gentamicin &<br>Oral Amoxicillin<br>7 injections | Gentamicin &<br>Pro. Pen inj<br>4 injections | Gentamicin &<br>Oral Amoxicillin<br>2 injections |
|---|--|--|--|--|
|   | n= 828   | n= 826   | n= 862                                       | n= 848   |
| <b>Treatment failure</b><br>(Risk Difference)       | 67 (8.1%)  | 51 (6.2%)<br>-2% (-4% to<br>0.1%)                | 65 (7.5%)<br>-1% (-3% to 2%)                 | 46 (5.4%)<br>-3% (-5% to 0.3%)                   |
| Death   | 10 (1.2%)  | 8 (1.0%)   | 17 (2.0%)                                    | 10 (1.2%)  |
| Clinical deterioration                              | 12 (1.4%)  | 11 (1.3%)  | 12 (1.4%)                                    | 15 (1.8%)  |
| SAE   | 1  | 0  | 0  | 0  |
| Hospitalization                                     | 2  | 2  | 4  | 1  |
| Not improved by day<br>4/ Not recovered by<br>day 8 | 42 (5.1%)  | 30 (3.6%)  | 32 (3.7%)                                    | 20 (2.4%)  |
| Death during 2<br>wks                               | 12 (1.4%)  | 10 (1.1%)  | 20 (2.3%)                                    | 11 (1.3%)  |

# **WHO Guideline for Management of PSBI**



- The attached publication in English and French with some information about the guideline can be accessed on our website
- <u>http://www.who.int/maternal\_child\_a</u> <u>dolescent/documents/bacterial-</u> <u>infection-infants/en/</u>
- ENGLISH http://apps.who.int/iris/bitstream/106 65/181426/1/9789241509268\_eng.p df?ua=1
- FRENCH http://apps.who.int/iris/bitstream/106
   65/205563/1/9789242509267\_fre.pd f?ua=1



# **Overall context**

- This guideline is for low resource settings in the context of primary health care only where referral is not possible
- The treatment guideline is for use by professionally trained health workers, and not for lay community health workers.
- The health workers should be appropriately trained, supplied with necessary equipment and medicines and supervised for the identification of signs of illness, referral, treatment if referral is not accepted and close follow up.
- Monitoring of the programme is essential for ensuring high quality of identification, treatment and follow up activities.
- These guidelines are expected to rationalize the use of antibiotics for young infants with suspected infection.
- Surveillance for antimicrobial resistance should be strengthened in all countries.



# **Target audience**

- National Policy-makers in health ministries
- Programme managers working in child health, essential drugs and health workers training
- Health care providers and clinicians managing sick children at various levels of health care including public and private
- Development partners providing financial and or technical support for child health programme



# **Objectives of the guideline**

- Provide recommendations on the use of antibiotics for neonates and young infants (0-59 days old) with PSBI in order to reduce mortality rates
- Provide clinical guidance on use of simple antibiotic regimens that are both safe and effective for outpatient treatment of clinically severe infection and fast breathing pneumonia
- Provide programmatic guidance on the role of CHW and home visits in identifying signs of PSBI



# **Postnatal Home visits by CHWs**

| Recommendation  | Strength of recommendation | Quality of<br>Evidence |
|---|----------------------------|------------------------|
| Home visits made as part of postnatal care,<br>CHWs should counsel families on<br>recognition of danger signs, assess young<br>infants for danger signs of illness and<br>promote appropriate care seeking. | Strong                     | Moderate               |



# Fast breathing pneumonia\*

| Recommendation  | Strength of recommendation | Quality<br>of<br>Evidence |
|---|----------------------------|---------------------------|
| Young infants 7-59 days old with fast breathing as<br>the only sign of illness should be treated with oral<br>amoxicillin, 50 mg/kg per dose twice daily for 7<br>days, by an appropriately trained health worker.  | Strong                     | Low                       |
| Infants 0-6 days with fast breathing as the only<br>sign of illness should be referred to hospital. If<br>referral is not accepted, they should be<br>treated with oral amoxicillin, 50 mg/kg per dose<br>twice daily for 7 days, by an appropriately trained<br>health worker. | Strong                     | Low                       |

\*Fast breathing 60 or more breaths per minutes



# **Clinical Severe Infection\***

| Recommendation   | Strength of recommendation | Quality of Evidence |
|--|----------------------------|---------------------|
| Young infants 0-59 days old with clinical severe<br>infection whose families do not accept or cannot<br>access hospital care should be managed in<br>outpatient settings by an appropriately trained                       |                            |                     |
| health worker with one of the following regimens:<br><u>Option 1</u> : IM gentamicin 5-7.5 mg/kg once daily for<br>7 days and twice daily oral amoxicillin, 50 mg/kg per<br>dose for 7 days. Close follow up is essential. | Strong                     | Moderate            |
| Option 2: IM gentamicin 5-7.5 mg/kg once daily for<br>2 days and twice daily oral amoxicillin, 50 mg/kg per<br>dose for 7 days. Close follow up is essential. A<br>careful assessment on day 4 is mandatory.               | Strong                     | Low                 |

\*Stopped feeding well, movement only when stimulated, severe chest in-drawing, Temperature  $\geq$  38.0°C or <35.5°C



# **Critical Illness\***

| Recommendation  | Strength of recommendation | Quality of<br>Evidence            |
|---|----------------------------|-----------------------------------|
| Young infants 0-59 days old who have any<br>sign of critical illness (at presentation or<br>developed during treatment of clinical<br>severe infection) should be hospitalized<br>after pre-referral treatment. | Strong                     | Very low<br>(Current<br>standard) |

\* unconscious, convulsions, inability to feed, inability to cry, apnoea, cyanosis, bulging fontanel, persistent vomiting, suspicion of meningitis



# Summary

- The guideline has the potential to increase access to treatment of PSBI in young infants
- The implementation of the guideline will:
  - contribute to the reduction of neonatal and young infant mortality
  - reduce inequity in access to care
  - provide an opportunity to improve home visits
- Needs to be implemented within the context of national health strategies, Every Newborn Action Plan and the available intervention packages – and <u>not as a vertical programme</u>
- Need for continuum of care at community, primary health care and referral facilities



# **Support to Country Implementation**

- Training materials
- Joint Statement by various partners
- Guideline for Operationalizing management of sick young infants with PSBI where referral is not feasible in the context of existing maternal, newborn and child health programmes
- Technical support





- The attached publication in English and French with some information about the guideline can be accessed on our website
- <u>http://www.who.int/maternal\_child\_a</u> <u>dolescent/documents/bacterial-</u> <u>infection-infants/en/</u>
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