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1.1 Acknowledgments

The authors acknowledge the valuable contributions made by the RETAPP Study Team:

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1.2 Deaths

1. 4 months old male baby, weight 5.975, active alert, feeding well, no previous history of illness, 7th baby of the family delivered through normal vaginal delivery at home, cried immediately after birth, no significant family history of convulsions or any other illness, baby was exclusively breast feed.

Enrolled with complaint of cough for 7 days and fever for 1 day. Respiratory rate was 64 breaths per minute (first reading), 64 breaths per minute (second reading), O2 saturation 99%, temperature 36.6 C, length 58.3/58.3cm, MUAC, 11.3/11.3 cm, vaccination incomplete (missed Pentavalent 3 and did not receive any dose of PCV).

After randomisation, received 5ml of study drug at 1120 hours and dropped home after explaining and providing number of on call physician. It was also explained when to return in case of any emergency.

Day 1_ November 6, 2016 at 0925 (Sunday) follow up conducted by CHW. On examination RR was 50/48/48, Temp 36C, O2 96%. Baby was well. Morning dose was given. Evening follow up and doses were also given by CHW in evening.

Day 2 _ November 7, 2016 at 1150 hours baby was seen at health center and was examined by study physician. RR was 38/47/47; Temp 36C, O2 95%, morning dose was given. Evening follow up was conducted by CHW, baby was well and dose was given.

Day 3_ November 8, 2016 at 1300 hours baby was examined at health center by study physician, RR was 43/35, Temp 36.9C, O2 99%. Baby was well.

Day 5_ November 10, 2016 at 1345 hours. Baby was examined at health center by study physician, was well with no active complaints, feeding well, with RR 33/34, Temp 36.9C, O2 94%. 

3
Day 14: November 19, 2016 As per schedule RETAPP CHW went to the baby’s home today for 14 day follow up and was told by mother that patient had expired on 14-11-16 (Monday at 0400 hours in the hospital – National Institute of Child Health).

On Sunday, November 13, 2016 at 1100 hours baby developed high grade fever with convulsions, involving his right upper and lower limb with uprolling of the eyes, and frothing from mouth. He was taken to a local GP who referred him to Indus hospital by that GP without giving any medication. Patient became unconscious while on the way to Indus Hospital. He reached at 1300 to Indus Hospital. Doctors at Indus Hospital gave him some IV fluids, injectable drugs (not given any documented paper, they do not know the names of the medication) and oxygen therapy. Meanwhile mother was told that baby became stiff at that moment and was then referred to NICH at 1430 hours. At NICH patient was again given injectable drugs (names not known), IV fluids and then was intubated. The family was given ambu bag to ventilate the baby because of shortage of space in the Intensive Care Unit. He was kept in the emergency the whole time and expired at 0400 hours on November 14, 2016.

It was enquired why mother didn’t contact on call physician and hospital number that was provided to her. She replied that she was confused to see the condition of the baby and forgot to call anyone. According to the mother they did not receive any discharge papers or treatment details. The death certificate mentioned cause of death is cardiopulmonary arrest secondary to pneumonia and sepsis.  

2. 15 months old female child, active alert, feeding well, no previous history of illness, 2nd child of the mother delivered through normal vaginal delivery at some hospital, cried immediately after birth, no significant family history of convulsions or any other illness. Length 73.8/cm, MUAC, 12.4/12.4 cm, vaccination incomplete (missed Pentavalent 3 and pneumococcal 3 and measles 1 and 2).

She was enrolled with complaints of cough for 2 days and fever for 1 day. Respiratory rate was 49 breaths per minute (first reading), 46 breaths per minute (second reading), O2 saturation 95%, temperature 40°C sponging done and Paracetamol given at the PHC, 2nd reading 38.6°C, (physician gave him Syp paracetamol 4hrly for home). After randomization, received 5ml of study drug at 1120 hours and dropped home after explaining and providing number of on call physician and local collector Data collector of the study site. It was also explained when to return in case of any emergency.

On Day 0, February 4, 2017 at 1811 hours evening follow up was conducted by CHW. On examination child had cough, RR was 44/46, Temp 36.7°C, O2 92% in air. She was well according to parents. Evening dose, 5 ml of study drug was given by CHW the child vomited out and this was repeated which she tolerated. Father complained that the child had cough so requested CHW for nebulization, so the CHW nebulized the child with normal saline at the PHC, and then dropped them back at home, after explaining
to call in case of any emergency. Evening physician took update from the CHW who informed about the vomiting.

According to the father, after 2 hours of nebulization, the child developed high grade fever (not documented), and another bout of cough so parents took her to a local health care provider (GP) who prescribed injections ceftriaxone and amikacin along with oral ventolin syrup. After the injectable, according to the father, the child was better for some time but between 0100-0200 hours on February 15th 2017, he had two episodes of small watery loose stool. Within 5 to 10 minutes of the episode, the baby got stiff and unresponsive. The father felt like the child had already died but for confirmation, they took him to Sultan Hospital from where child was referred to Chinniot Hospital where the doctor declared death on arrival. Later, we asked the father why the on call physician was not contacted, to which they replied that they forgot to call. Based on the father’s narrative, the child had died around 0200 hours at home.
1.3 Supplementary Table

Table S1: Comparison of No treatment Failure and Treatment failure (by Day 3) by Baseline Characteristics of Patients Completed per Protocol Treatment (n=3856) using mixed model approach

|                              | No treatment failure | Treatment failure | OR (95% CI) |
|------------------------------|----------------------|-------------------|-------------|
| **Treatment**                |                      |                   |             |
| Amoxicillin                  | 1878/3710(50.6)      | 51/146(34.9)      | Ref.        |
| Placebo                      | 1832/3710(49.4)      | 95/146(65.1)      | 1.87(1.27,2.75)** |
| **Demographic Indicators**  |                      |                   |             |
| Sex                          |                      |                   |             |
| Male                         | 1948/3710(52.5)      | 82/146(56.2)      | 1.08(0.74,1.58) |
| Age categories in month      |                      |                   |             |
| 2-11                         | 1707/3710(46.0)      | 70/146(48.0)      | Ref.        |
| 12-59                        | 2003/3710(54.0)      | 76/146(52.1)      | 0.98(0.67,1.43) |
| Maternal years of schooling  |                      |                   |             |
| No education                 | 2329/3710(62.8)      | 88/146(60.3)      | 1.28(0.31,5.33) |
| 1-5 years                    | 521/3710(14.0)       | 22/146(15.1)      | 1.20(0.27,5.37) |
| 6-10 years                   | 746/3710(20.1)       | 31/146(21.2)      | 1.32(0.30,5.80) |
| Above 10 years               | 114/3710(3.1)        | 5/146(3.4)        | Ref.        |
| **History of reported**      |                      |                   |             |
| Diarrhoea                    | 280/3710(7.6)        | 19/146(13.0)      | 2.07(1.16,3.70)** |
| Fever                        | 2164/3710(58.3)      | 110/146(75.3)     | 2.22(1.43,3.45)** |
| Cough                        | 3683/3710(99.3)      | 145/146(99.3)     | *           |
| Fast/difficult breathing     | 2387/3710(64.3)      | 104/146(71.2)     | 1.34(0.89,2.02) |
| Chest in-drawing             | 47/3710(1.3)         | 2/146(1.4)        | 0.89(0.12,6.56) |
| URTI                         | 1397/3710(37.7)      | 55/146(37.7)      | 1.23(0.84,1.81) |
| Vomiting                     | 63/3710(1.7)         | 3/146(2.1)        | 0.62(0.08,4.56) |
| Measles(within last 3 month) | 26/3710(0.7)         | 1/146(0.7)        | *           |
| **Breastfeeding with age categories** |                  |                   |             |
| 2-5 month                    | 1023/1069(95.7)      | 44/44(100.0)      | *           |
| 6-11 month                   | 616/637(96.7)        | 22/26(84.6)       | *           |
| 12-24 month                  | 956/1007(94.9)       | 44/45(97.8)       | *           |
| **Immunization** b           |                      |                   |             |
| Upto date immunization       | 1838/3710(49.5)      | 61/146(41.8)      | 0.69(0.47,1.02) |
| Upto date PCV and Penta      | 2293/3710(61.8)      | 89/146(61.0)      | 0.97(0.65,1.42) |
| **Physical Examination**     |                      |                   |             |
| Anaemia                      | 369/3710(10.0)       | 23/146(15.8)      | 1.60(0.93,2.76) |
| MUAC <11.5 cm a              | 80/2641(3.0)         | 4/102(3.9)        | 0.39(0.05,3.27) |
| Stunting(HAZ<-2 SD)          | 1687/3684(45.8)      | 71/144(49.3)      | 1.41(0.96,2.07) |
| Wasting(WHZ<-2SD)            | 664/3673(18.1)       | 30/142(21.1)      | 0.94(0.57,1.56) |
|                                | No treatment failure | Treatment failure | OR (95% CI) |
|--------------------------------|----------------------|-------------------|-------------|
| Under-weight (WAZ < -2SD)      | 1543/3703 (41.7)     | 67/145 (46.2)     | 1.11 (0.76, 1.64) |
| Temperature >=37.5 °C          | 1175/3710 (31.7)     | 74/146 (50.7)     | 2.49 (1.70, 3.65)** |

**RR child**

| Group  | Count/Total (Percentage) | Count/Total (Percentage) | OR (95% CI) |
|--------|--------------------------|--------------------------|-------------|
|        |                          |                          |             |
| 40-49  | 1620/2003 (80.9)         | 53/76 (69.7)             | Ref.        |
| 50-59  | 334/2003 (16.7)          | 19/76 (25.0)             | 2.29 (1.01, 5.21)** |
| 60-69  | 44/2003 (2.2)            | 3/76 (4.0)               | 3.00 (0.65, 13.87) |
| >=70   | 5/2003 (0.3)             | 1/76 (1.3)               | 8.25 (0.40, 170.86) |

**RR Infant**

| Group  | Count/Total (Percentage) | Count/Total (Percentage) | OR (95% CI) |
|--------|--------------------------|--------------------------|-------------|
| 50-59  | 1463/1707 (85.7)         | 51/70 (72.9)             | Ref.        |
| 60-69  | 221/1707 (13.0)          | 15/70 (21.4)             | 3.42 (0.69, 16.84) |
| 70-79  | 20/1707 (1.2)            | 3/70 (4.3)               | 2.61 (0.20, 34.12) |
| >=80   | 3/1707 (0.2)             | 1/70 (1.4)               |              |

**Oxygen Saturation**

| Group  | Count/Total (Percentage) | Count/Total (Percentage) | OR (95% CI) |
|--------|--------------------------|--------------------------|-------------|
| 90-92  | 467/3710 (12.6)          | 23/146 (15.8)            | Ref.        |
| 93-95  | 990/3710 (26.7)          | 44/146 (30.1)            | 0.89 (0.49, 1.63) |
| >95    | 2253/3710 (60.7)         | 79/146 (54.1)            | 0.72 (0.41, 1.24) |

**Wheeze**

| Count/Total (Percentage) | Count/Total (Percentage) | OR (95% CI) |
|--------------------------|--------------------------|-------------|
|                          |                          |             |

**Household demographics**

|                                | Count/Total (Percentage) | Count/Total (Percentage) | OR (95% CI) |
|                                |                          |                          |             |
| HH with improved drinking water| 3388/3710 (91.3)         | 130/146 (89.0)           | 0.68 (0.39, 1.19) |
| HH with improved sanitation facilities | 3406/3710 (91.8) | 137/146 (93.8) | 1.68 (0.73, 3.85) |

**HH indoor air quality**

|                                | Count/Total (Percentage) | Count/Total (Percentage) | OR (95% CI) |
|                                |                          |                          |             |
| Good                           | 1991/3710 (53.7)         | 61/146 (41.8)            | Ref.        |
| Moderate                       | 625/3710 (16.9)          | 38/146 (26.0)            | 1.92 (1.21, 3.03)** |
| Poor                           | 1094/3710 (29.5)         | 47/146 (32.2)            | 1.03 (0.65, 1.65) |

**These variables were included in the final multivariate model**

*Model not converged with very high and low indicator/outcome distribution*
# CONSORT Statement 2006- Checklist for Non-inferiority and Equivalence Trials

Items to include when reporting a non-inferiority or equivalence randomized trial

| PAPER SECTION And topic | Item | Descriptor | Reported on Page # |
|-------------------------|------|------------|--------------------|
| TITLE & ABSTRACT        | 1    | How participants were allocated to interventions *(e.g., "random allocation", "randomized", or "randomly assigned")*, specifying that the trial is a non-inferiority or equivalence trial. | 1, 3, 4 |
| INTRODUCTION Background | 2    | Scientific background and explanation of rationale, including the rationale for using a non-inferiority or equivalence design. | 5, 6, 7 |
| METHODS Participants    | 3    | Eligibility criteria for participants *(detailing whether participants in the non-inferiority or equivalence trial are similar to those in any trial(s) that established efficacy of the reference treatment)* and the settings and locations where the data were collected. | 7, 8 |
| Interventions           | 4    | Precise details of the interventions intended for each group detailing whether the reference treatment in the non-inferiority or equivalence trial is identical (or very similar) to that in any trial(s) that established efficacy, and how and when they were actually administered. | 8, 9 |
| Objectives | 5 | **Specific objectives and hypotheses**, including the hypothesis concerning non-inferiority or equivalence. | 10 |
| Outcomes | 6 | Clearly defined primary and secondary outcome measures detailing whether the outcomes in the non-inferiority or equivalence trial are identical (or very similar) to those in any trial(s) that established efficacy of the reference treatment and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors). | 10 |
| Sample size | 7 | How sample size was determined detailing whether it was calculated using a non-inferiority or equivalence criterion and specifying the margin of equivalence with the rationale for its choice. When applicable, explanation of any interim analyses and stopping rules (and whether related to a non-inferiority or equivalence hypothesis). | 10,11 |
| Randomization -- Sequence generation | 8 | Method used to generate the random allocation sequence, including details of any restrictions (e.g., blocking, stratification) | 8,9 |
| Randomization -- Allocation concealment | 9 | Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned. | 9 |
| Randomization -- Implementation | 10 | Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups. | 9 |
| Blinding (masking) | 11 | Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated. | 9 |
| Statistical methods | 12 | Statistical methods used to compare groups for primary outcome(s), specifying whether a one or two-sided confidence interval approach was used. Methods for additional analyses, such as subgroup analyses and adjusted analyses. | 11,12 |
| RESULTS | 13 | Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons. | 12,13 |
| Participant flow | 14 | Dates defining the periods of recruitment and follow-up. | 12 |
Baseline data

Baseline demographic and clinical characteristics of each group.

Table 1

Numbers analyzed

Number of participants (denominator) in each group included in each analysis and whether the analysis was “intention-to-treat” and/or alternative analyses were conducted. State the results in absolute numbers when feasible (e.g., 10/20, not 50%).

12

Outcomes and estimation

For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g., 95% confidence interval). For the outcome(s) for which non-inferiority or equivalence is hypothesized, a figure showing confidence intervals and margins of equivalence may be useful.

Table 2

Ancillary analyses

Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.

Table 3, 4, 5

Adverse events

All important adverse events or side effects in each intervention group.

Table 2

DISCUSSION

Interpretation

Interpretation of the results, taking into account the non-inferiority or equivalence hypothesis and any other study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.

16, 17, 18

Generalizability

Generalizability (external validity) of the trial findings.

19

Overall evidence

General interpretation of the results in the context of current evidence.

19, 20

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