RANDOMIZED CLINICAL TRIAL ON THE EFFECT OF PROBIOTIC, OHHIRA OMX CAPSULES, AS AN ADJUNCT IN THE TREATMENT OF SEVERE PNEUMONIA IN PATIENTS 6-24 MONTHS OF AGE

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ABSTRACT

BACKGROUND: Probiotics are live microorganisms which stimulate the growth of another which upon ingested in sufficient number can exert health effects beyond inherent basic nutrition." Health effects attributed were lower frequency and duration of diarrhea, stimulation of humoral and cellular immunity, and reduction of unfavorable metabolites in the colon. However, there are limited studies in the effects of these probiotics in respiratory tract infections in humans both local and international.
OBJECTIVE: To determine the efficacy of a probiotic, OMX Ohhira capsules, as an adjunct in the treatment of severe pneumonia in patients 6-24 months old.
DESIGN: Randomized Clinical Trial
SETTING: A government tertiary hospital in Manila, Philippines
SUBJECTS: 76 infants 6-24 months old with severe pneumonia, without previous antimicrobial therapy and no co-morbidities: 40 in the intervention group and 36 in the control group.
METHODS: Subjects enrolled were randomized to IV Ampicillin at 100mg/kg/day plus OMX Ohhira capsules 1 capsule 2x/day or IV Ampicillin alone. The duration of illness, previous treatment and illnesses, other signs and symptoms and vaccinations were recorded. Side effects were also noted. T test and Chi square test were used in the analysis of variables of both groups. All tests of significance were carried out at <0.05 level of significance and 95% confidence interval. Risk assumptions were estimated using EPI Info Stat Calc Version 2000. The magnitude of treatment effects (RR, ARR, RRR, NNT) was also computed. The outcome assessor was blinded as to the treatment groups.
OUTCOME MEASURES: Number of days with cough, tachypnea, retraction and fever, presence of hypoxemia, return to usual feeding, shift of IV antibiotic to oral preparation or another IV antibiotics, length of hospital stay and subgroup of patients without any other drugs taken previously.
RESULTS: Patients in the probiotic group had shorter duration of cough and hospital stay with mean/SD 2.4+/-1 day compared to control with a mean/ SD 4.3+/-1days (p value <0.007). Resolution of tachypnea for age and retractions had a mean/SD 1.5+/-0.5 days in the intervention group compared to the control with mean/SD 4.3+/-1days (p value <0.001).). Improvement of appetite had a mean/SD 1.0+/-0.2day in the intervention group compared to the control with mean/SD 2+/-1days (p value <0.001). One patient in the treatment group who developed rashes after taking the drug eventually dropped out. On day 3 of the trial, 2 patients (5%) in the probiotic group compared to 17 patients (47%) were still tachypneic, with RR of 0.11, RRR of 0.89, ARR of 0.42 and NNT of 2. Only 1 patient (2%) in the treatment group had increased infiltrates on repeat CXR on day 3 of treatment compared to 13 patients (36%) in the control group. Shifting to another IV antibiotics was not statistically different.
CONCLUSION: The use of probiotics significantly shortened the duration of cough and hospital stay even with no previous adjunct therapy (mean of 2.4 days in the treatment group vs. 4.3 days in the control group). Observable clinical significance had shorter mean day of onset of resolution for tachypnea for age, cough, fever, rales, retractions, wheezing, improvement in appetite and shortened hospital stay among those given intravenous Ampicillin plus OMX capsules.

INTRODUCTION

Probiotic is derived from the Greek words "pro" meaning "for" and "bios" meaning "life". It was used by Lilly and Stilwell in 1965 to describe live substances of human origin secreted by one microorganism which stimulates the growth of another which upon ingested in sufficient number can exert health effects beyond inherent basic nutrition." Health effects attributed were lower frequency and duration of diarrhea, stimulation of humoral and

cellular immunity, and reduction of unfavorable metabolites in the colon. However, there are limited studies in the effects of these probiotics in respiratory tract infections in humans.

Pneumonia remains to be the most common cause of morbidity and mortality among infants and children worldwide. According to the latest Department of Health data 2002, 0.9% or 924/100,000 population had pneumonia making it the top leading cause of morbidity. Cases were viral, bacterial, fungal or atypical. In our institution, it is among the top 3 leading causes of consultation (52%), admission (32%) and deaths (22%) in 2004.

Pneumonia, according to the Control of Acute Respiratory Infection (CARI) Protocol of the World Health Organization (WHO) is defined as cough associated with tachypnea depending on age group; >60/min for less than 2 months old, >50/min for 2-12months old and >40/min for 1-5 years old. If associated with chest indrawing or stridor, it is categorized as severe pneumonia.

Sickness may occur if there are disturbances in our microbial balance. We have billions of good bacteria populating our intestinal tract. These friendly bacteria form a protective barrier to keep bad bacteria out maintaining a healthy intestinal tract. Use of antibiotics, steroids, chlorinated drinking water, high fat and high sugar diet are all devastating to the gut. However, colonization of the gut with appropriate microflora constitute to its ability to function normally. Some of these were Lactobacillus and Bifidobacterium species that can prevent food decay, preserve antioxidant and vitamins, remove toxic food components and prevent pathogenesis of Enterobacteriaceae, Staphylococcus aureus and enterococcus found in fermented food. Probiotics are live microbial food supplements that beneficially affect humans by improving intestinal microbial balance. They modulate not only the endogenous flora of the gastrointestinal tract but also the immune system. Lactobacilli and bifidobacteria augment both cellular and humoral immunity. Lactic acid- producing bacteria stimulate various aspects of the immune system including phagocytic function of macrophages, natural killer cells, monocytes and neutrophils. Probiotics bacteria, therefore favorably alters the intestinal microbial balance, inhibits the growth of harmful bacteria, promotes good digestion, boosts immune function and increase resistance to infection.

Probiotic treatment has been shown to be efficacious in a variety of disease states such as diarrhea, constipation, Ulcerative Colitis and Crohn's disease but there are no sufficient studies done yet on its benefits on respiratory tract infections internationally and locally. Several studies have proven the benefits of probiotics in the treatment of diarrheal diseases. A local study done by Orendain, Franco and Gatcheco in 1999 revealed that Infloran Berna, a probiotic, was effective in shortening the duration of diarrhea in children less than 5 years old (mean duration: 3.4 days vs. 4.12 days in the control group). A similar study done by Oandasan, Gatcheco and Kapalungan showed the same beneficial effect. Another study done by Salazar- Lindo et al in Peru in 2004, utilized Lactobacillus casei strain GG in milk formula among 179 male infants 3-36 months old. However, it did not show positive effect on the clinical course of acute watery diarrhea probably due to transient lactose malabsorption. Only few studies were done on its uses in respiratory tract infections. In a study done in Switzerland by Gluck and Gebber in 2003, they utilized fermented milk with lactobacilli and bifidobacterium daily for 3 weeks. Results showed it reduced nasal

colonization of potentially pathogenic bacteria such as Staphylcoccus aureus, Streptococcus pneumonia, and Beta hemolytic streptococcus, however, this study was done in adults 30-40 years old.

Another probiotic showing potential benefits is now locally available for consumption. It is the OMX Ohhira capsule, named after Dr. Iichiroh Ohhira, a microbiologist from Okayama, Japan. It was developed in 1980 and named as "Japan's Best New Product" in 1991. It is a food medicine which beneficially improves and restores altered human intestinal microbial balance. This is an enteric coated paste-form capsule that contains 12 strains of Lactobacillus and Bifidus bacteria, 18 amino acids, Vitamin B- complex, minerals and anti- oxidants. It aims to maintain and restore intestinal microbial balance after treatment with antibiotics, infectious diarrhea and other factors that destroy the intestinal microflora. It can resist stomach acidity, hence effective in normalizing the microflora (Lactic acid bacteria) in the intestinal tract. It stabilizes the colon's optimum pH level and suppresses the growth of bad bacteria while stimulating the immune system. It has been proven clinically to inhibit Staphylococcus aureus, H. pylori and E. coli which are now sometimes resistant to antibiotics. Being in capsule form, can easily be handled, needs no refrigeration and has a shelf life of 3 years. A local study done by Valdoria and Gatcheco in 2005 utilized OMX capsules in 3-24 months old patients with acute non bloody diarrhea which showed shorter duration of diarrhea, 3.17 days compared to 5.24 days in the control group.

SIGNIFICANCE

This study can provide information on a possible adjunctive effect in the treatment of severe pneumonia to further decrease the incidence, severity of symptoms, deaths and length of hospital stay.

Available information is limited as to the potential role of probiotics in infants and children with Respiratory tract infections compared to diarrheal diseases. If antibiotics are the miracle medicine of the 20th century, probiotics is for the 21st century. Within every human being is a flourishing living colony of approximately four pounds of bacteria. Most of these bacteria reside in human digestive tract. In the absence of sufficient number of friendly bacteria known as "probiotics", human life could not exist. When humans fail to maintain sufficient number of good bacteria in the body, disease will occur and death likely may follow.

OBJECTIVES

General Objective:

To determine the efficacy of probiotics, Ohhira OMX capsules, as an adjunct treatment to severe pneumonia in patients 6-24 months old.

Specific Objectives:

1. To describe the clinical and sociodemographic profile of infants 6-24 months old admitted with severe pneumonia.
2. To establish and compare the effectiveness of probiotics, Ohhira OMX capsules, given 1 capsule 2x/day for 5days 3 hours after injection of intravenous Ampicillin vs. Ampicillin alone in terms of:
    a. Decreased respiratory rate
    b. Improvement of retractions or chest indrawing
    c. Hypoxemia based on pulse oxymeter readings
    d. improved appetite
    e. resolution of fever
    f. shift of IV antibiotics to oral preparation
    g. shift of Ampicillin to another IV antibiotics
    h. length of hospital stay
    i. improvement in WBC count and CXR on 3rd day of treatment
3. To determine the adverse effects associated with the use of probiotic

Operational Definition of Terms:

- Improvement in the respiratory rate in this study is defined as minimum number of days in terms of return to normal rate for age: <50/min for 6-12 months old and <40/min for 12-24 months old.
- Improvement of retraction or chest indrawing is the minimum number of days in the resolution of retraction.
- Hypoxemia is defined as oxygen saturation less than 90 percent using a pulse oxymeter.
- Improved appetite in this study is defined as the earliest time in days in the return to usual feeding habits.
- Resolution of fever (if present) is defined as the earliest time in days that temperature maintained at 36.5-37.5 C.
- Shift of IV Ampicillin to oral preparation is defined as the earliest number of days medication was shifted.
- Length of hospital stay is defined in this study as the number of days from admission until discharge from the hospital.
- Treatment failure is defined as those patients unimproved on the 3rd day of treatment and shifted to IV Cefuroxime.

PATIENTS AND METHODS

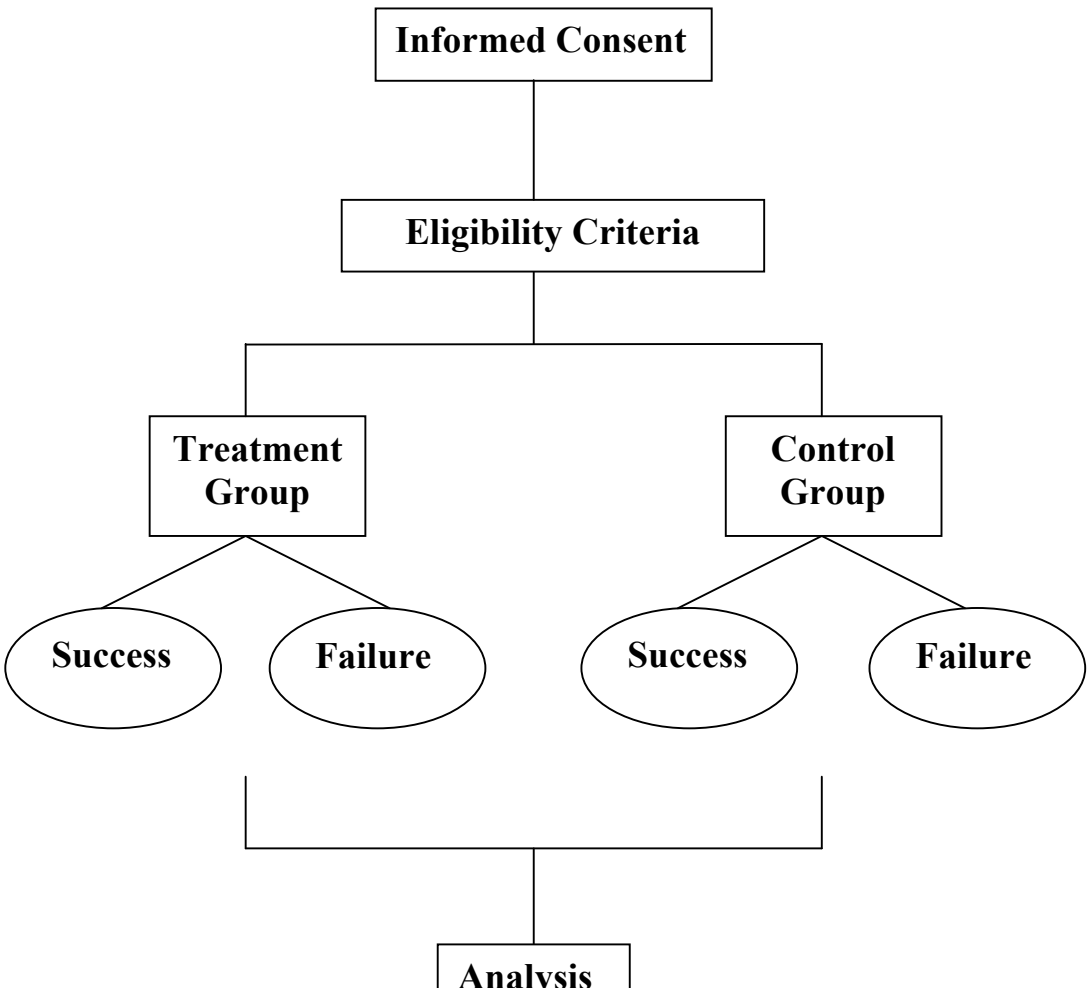
This study was a randomized clinical trial. The study population consisted of 76 infants, 6 to 24 months of age, brought to the emergency room and was subsequently admitted due to severe pneumonia based on the WHO-ARI protocol. Excluded in this study were infants presenting with very severe pneumonia, other co-morbidities such as septicemia, heart disease, severe dehydration, severe malnutrition, had GI surgery such as colostomy, and given adequate dose of oral antibiotics within the last 72 hours.

All parents or caregivers of the admitted patients were informed of the benefits and possible adverse effects of OMX capsule. They signed a consent form prior to enrolment to the research project. The ER doctor on duty randomized the subjects using table of random numbers. They were randomized into 2 groups. Group A was given Ohhira OMX capsules, 1 capsule paste-form twice a day for 5 days three hours after intravenous Ampicillin at 100mg/kg/day while Group B was only given IV Ampicillin alone. Admitting doctors instructed the care givers to prick the capsule and give its contents directly by mouth to the patients.

Upon admission, complete history and physical examination were taken including the age, sex, vital signs, anthropometric measurements, feeding and nutritional history, immunization status, associated signs and symptoms and past illnesses. Complete blood count with platelet count (CBC PC) and Chest X-ray (CXR) were also done. Each patient was endorsed to the doctors in charge of the Pulmonology ward, who also supervised the giving of medications. The investigators were blinded as to whether the subjects were given the probiotic or not.

A five- day treatment was allotted for each patient, being assessed on 6- hour intervals. However, the third day of the treatment was critical because patients were reassessed in terms of clinical improvements such as resolution of tachypnea, retractions and fever and return to usual feeding habits. Laboratory parameters were also reassessed by a repeat CBC with PC and CXR. If at this time, the patient improved, IV Ampicillin was shifted to oral Amoxicillin and may possibly be discharged from the hospital the following day. However, if the patient was not improving, IV Ampicillin was shifted to IV Cefuroxime and these patients were categorized as "treatment failure".

Figure 1.0 Conceptual framework of the Methodology



STATISTICAL ANALYSIS

All numerical data were summarized using measures of central tendency (mean and standard deviation). All categorical variables were summarized using percentage-frequency distribution and were compared using chi-square. All comparison of outcomes which were numerical in nature (mean days of onset of resolution of symptoms) were compared using T-test for independent samples. The size of the effect was expressed as relative Risk (RR) with its 95% confidence interval.

Tests for homoegeneity of sample were carried out using the two aforementioned tests. The size of the effect was expressed as Relative Risk (RR) with its 95% Confidence Interval. The corresponding Relative Risk Reduction (RRR), Absolute Risk Reduction (ARR) and Number Needed to Treat (NTT) were computed.

All tests of significance were carried out at .05 level of significance and 95% CI, using the licensed statistical software SPSS version 10.1 (STATISICAL PACKAGE FOR THE SOCIAL SCIENCES) while the risk assumptions were estimated using EPI Info Stat Calc, version 2000.

RESULTS

Socio-demographic Profile:

A total of 76 subjects met the inclusion and none of the exclusion criteria. There was one patient receiving the treatment who dropped-out. This was a nine-month old infant who developed rashes after receiving the treatment. Intention to treat analysis revealed no significant effect brought about by this drop- out. The baseline characteristics of the subjects are summarized in Table-1.

There was a statistically significant higher mean age observed in the treatment group (11 vs. 8 months old, $p<.001$). No significant difference exists in terms of the sex-distribution and geographic location ($p=0.33$).

Table-1 **Baseline Socio-demographic Profile of Children Randomized to OMX Capsules with IV Ampicillin vs IV Ampicillin alone, A Randomized Controlled Trial, 2005**

Characteristic		OMX + IV Ampicillin N=40		IV Ampicillin only N=36,		p-value*
		N	%	N	%	
Age (months)						
Range		7 – 24		6 – 12		***<.001*** **
Mean ± SD		11 ± 3		8 ± 2		
Sex:	Male	**25**	62.5	**23**	63.9	
	Female	**15**	37.5	**13**	36.1	.90
	Total	***40***	*100*	***36***	*100*	
Location:	Tondo	**13**	32.5	**7**	19.4	
	Navotas	**0**	--	**3**	8.3	
	Malabon	**3**	7.5	**6**	16.7	.33***
	Sta. Cuz	**4**	10	**2**	5.6	
	Quezon city	**3**	7.5	**3**	8.3	
	Caloocan	**8**	20	**5**	13.9	
	Pasay	**2**	5	**3**	8.3	
	Bulacan	**0**	--	**1**	2.8	
	Sampaloc	**2**	5	**2**	5.6	
	Valenzuela	**3**	7.5	**0**	--	
	Paco	**0**	--	**1**	2.8	
	Paranaque	**2**	5	**1**	2.8	
	Sta. Ana	**0**	--	**1**	2.8	
	Malate	**0**	--	**1**	2.8	
	Total	**40**	100	**36**	100	

*significant difference if p-value is <.05
** computed using independent samples T-test
*** computed using Chi-square Test, SPSS Version 10

Baseline Anthropometric Profile & Past Medical History

The homogeneity of the sample was also tested in terms of the patients' baseline anthropometric profile. (Table-2)

The two groups did not differ significantly in terms of weight (p=.31), length (p=.22), the presence or absence of stunting (p=.34) and the presence or absence of wasting (p=0.91).

The two groups also did not statistically differ in the proportion of co-morbidities and past history of pneumonia. (all p-values >.05)

Table-2 **Baseline Anthropometric Profile & Medical History of Children Randomized to OMX with IV Ampicillin vs IV Ampicillin alone, A Randomized Controlled Trial, 2005**

Characteristic	OMX + IV Ampicillin N=40		IV Ampicillin only N=36,		p-value*
	N	%	N	%	
Weight (kg) Mean ± SD	8.4 ± 1.2		7.2 ± 1.3		.31**
Length (cm) Mean ± SD	98.9 ± 8		74.5 ± 16		.22**
Stunting					
Present	**2**	2.5	**2**	8.3	.34***
Absent	**38**	97.5	**34**	91.7	
Wasting					
Present	**3**	5	**3**	5.6	.91***
Absent	**37**	95	**33**	94.4	
Past History of Pneumonia					
Present	**8**	20	**8**	22.2	.81***
Absent	**32**	80	**28**	77.8	
Other co-morbidities					
Asthma	**2**	5	**1**	2.8	.75***
Meningitis	**1**	2.5	**1**	2.8	
Sepsis	**1**	2.5	**0**	--	
None	**36**	90	**34**	94.4	
Total	**40**	100	***36***	100	

*significant difference if p-value is <.05
** computed using independent samples T-test
*** computed using Chi-square Test, SPSS Version 10

Profile of Children in terms of Signs and Symptoms of Pneumonia and Treatment Regimen

There was no observable difference in the mean days of illness prior to randomization between the two groups (3 days versus 4 days, p=.10).

All children had cough, chest in-drawing and rapid breathing. There was no statistical difference in terms of the presence of colds, anorexia, vomiting and fever between the two groups (all p-values > .05). The two groups did not differ significantly in terms of the proportion of patients with and without diarrhea. However a statistically higher percentage of patients with anorexia under the treatment arm was noted as compared to those in the control. (p<.001).

Table-3 **Signs and Symptoms, Duration of Illness of Children Randomized to OMX with IV Ampicillin vs IV Ampicillin alone, A Randomized Controlled Trial, 2005**

Characteristic	OMX + IV Ampicillin N=40		IV Ampicillin only N=36,		p-value*
	N	%	N	%	
Duration of illness					

(days)					
Range	1 - 6		2- 6		
Mean ± SD	3 ± 1		4 ± 1		.10**
Cough					
Present	**40**	100	**36**	100	--
Colds					
Present	**33**	82.5	**33**	91.7	.23***
Absent	**7**	17.5	**3**	8.3	
Fast breathing					
Present	**40**	100	**36**	100	--
Chest in-drawing					
Present	**40**	100	**36**	100	--
Fever					
Present	**28**	70	**33**	91.7	.33***
Absent	**12**	30	**3**	8.3	
Vomiting					
Present	**8**	20	**7**	19.4	.95***
Absent	**32**	80	**29**	80.6	
Loose bowel movement					
Present	**3**	8.1	**3**	8.3	.89***
Absent	**37**	92.5	**33**	91.6	
Anorexia					
Present	**12**	70	**0**	--	***.<.001****
Absent	**28**	30	**36**	100	
WBC Count			7.8 - 21		.52**
Range	6 – 20		12 ± 3		
Mean ± SD	11.3 ± 4				
Initial Chest Xray	40 (100)		36 (100)		--

*significant difference if p-value is <.05
** computed using independent samples T-test
*** computed using Chi-square Test, SPSS Version 10

Clinical Signs and Symptoms, Adjunct Medicines and Correctness of Dosing

Table-4 shows that there is no observed clinical difference in terms of the type of medications being used by the patients (p=.31). Mean duration of medication intake did not differ statistically between the treatment arm and control arm. Both arms were comparable in terms of the correct dosages of paracetamol, PPA, carbocisteine, salbutamol and ambroxol. (p=.23) A higher percentage of patients randomized to the control arm had more episodes of shifting to other intravenous antibiotic (Cefuroxime) (p-values<.001) on the third day of the experiment.

Table-4 **Treatment regimen of Children Randomized to OMX with IV Ampicillin vs IV Ampicillin alone, A Randomized Controlled Trial, 2005**

Characteristic	**OMX + IV Ampicillin N=40**		**IV Ampicillin only N=36,**		**p-value***
	N	**%**	**N**	**%**	
Duration of Medication Use					.89**
Mean ± SD	3 ± 1		3 ± 1		
Type of Medicine					
Phenylpropanolamine	**0**	0	**1**	2.8	
Ambroxol	**4**	10	**4**	11.1	.31***

Carbocisteine	**4**	10	**3**	8.3	
Paracetamol	**25**	62.5	**21**	58.3	
Salbutamol	**1**	2.5	**5**	13.9	
None	**6**	15	**2**	5.6	
Correctness of Doses					
Yes	**33**	82.5	**33**	91.7	.23***
No	**7**	17.5	**3**	8.3	
Shifting to other IV Antibiotics					
Yes at 2nd day	**1**	2.5	**8**	22.2	***.001******
Yes at 2.5 days	**0**	0	**1**	2.8	
Yes at 3 days	**0**	0	**11**	30.6	
No	**39**	97.5	**16**	44.4	
Shifting of IV to oral antibiotics					
On the 2nd day	**24**	60	**3**	8.3	***..001******
On the 3rd day	**12**	30	**8**	22.2	
On the 4th day	**4**	10	**14**	36.1	
On the 5th day	**0**	--	**3**	11.1	
On the 6th day	**0**	--	**7**	19.4	
On the 7th day	**0**	--	**1**	2.8	
Total	**40**	100	**36**	100	

*significant difference if p-value is <.05
** computed using independent samples T-test
*** computed using Chi-square Test, SPSS Version 10

Feeding Practices:

Comparing the two groups in terms of feeding practices, they did not differ statistically in the proportion of children on breastfeeding and mixed feeding (p=.17 and p=.62 respectively).

Age when solid foods were introduced was statistically significantly higher among those randomized to the control group. (6 versus 4, p=.03) (Table-5)

Table-5 **Baseline Feeding Practices of Children Randomized to OMX with IV Ampicillin vs. IV Ampicillin only, A Randomized Controlled Trial, 2005**

Characteristic	OMX + IV Ampicillin N=40		IV Ampicillin only N=36		p-value*
	N	%	N	%	
Breastfeeding					
Yes	**28**	70	**30**	83.3	.17***
No	**12**	30	**6**	16.7	
Mixed feeding					
Yes	**26**	65	**26**	72.2	.62***
No	**14**	35	**10**	27.8	
Age at solid food (months)					
Mean ± SD	5.4 ± 1		6 ± 1		***.03****

*significant difference if p-value is <.05

** computed using independent samples T-test
*** computed using Chi-square Test, SPSS Version 10

Immunization Status

The two groups did not significantly differ in terms of the proportion of children who completed, who did not complete or who did not receive any vaccinations for DPT, Oral polio, Hepatitis B, Hemophilus influenzae, measles, mumps and rubella and the standard measles vaccine (all p-values were >.05) (See table-6).

Table-6 **Baseline Immunization Status of Children Randomized to OMX with IV Ampicillin vs. IV Ampicillin only, A Randomized Controlled Trial, 2005**

Characteristic		OMX + IV Ampicillin N=40		IV Ampicillin only N=36,		p-value*
		N	%	N	%	
BCG	Present	**40**	100	**36**	100	--
DPT	Complete	**38**	95	**32**	88	
	Incomplete	**1**	2.5	**4**	22	.23***
	None	**1**	2.5	**0**	0	
OPV	Complete	**36**	90	**31**	86.1	
	Incomplete	**2**	5	**4**	11	.68***
	None	**2**	5	**1**	2.7	
Hepatitis B (3 doses)						
	Complete	**2**	5	**3**	8.3	.98***
	Incomplete	**9**	22.5	**7**	19.4	
	None	**29**	72.5	**26**	72	
Anti-measles	Yes	**11**	28.2	**16**	44.4	
	No	**28**	71.8	**20**	55.6	.14***
H. influenzae (Hib)	Yes	**3**	3	**1**	2.7	
	No	**36**	97	**35**	97.2	.34***
MMR	Yes	**0**	--	**1**	2.7	
	No	**40**	100	**35**	97.2	.29***

*significant difference if p-value is <.05
** computed using independent samples T-test
*** computed using Chi-square Test, SPSS Version 10

Effectiveness of OHHIRA-OMX in Pneumonia

The effectiveness of OHHIRA-OMX capsules was assessed in terms of the mean days of onset of resolution of specific symptoms, presence or absence of hypoxemia and length of hospital stay. No deaths were observed in this trial. One patient randomized to the treatment arm developed rash and eventually dropped out from the study. (Table-7)

Results show that patients with pneumonia treated with standard antibiotics plus OHHIRA-OMX capsules had statistically shorter mean days of onset of resolution of signs and symptoms of pneumonia compared to placebo. Mean day of resolution of tachypnea as gauged per age was significantly shorter (1.5 days versus 3 days, p<.001), days of fever (1 day versus 2 days, p<.001), retractions (1.5 days versus 3 days, p<.001), rales (2.3 days versus 3.4 days, p<.001), improvement of appetite was seen as early as 1 day post treatment versus 2 days with placebo (p<.001).

Mean days for resolution of cough and mean hospital stay were both statistically different between the two groups (both 2.4 days vs 4.3 days, p-values=<.007).

Table-7 **Mean Days of Onset of Resolution of Signs & Symptoms Among Children with Pneumonia, Randomized to OMX with IV Ampicillin vs IV Ampicillin alone, A Randomized Controlled Trial, 2005**

Characteristic	OMX + IV Ampicillin N=40	IV Ampicillin Only N=36	p-value*
Tachypnea for age Mean ± SD	1.5 ± 0.5	3 ± 1	***<.001*****
Fever Mean ± SD	1.0 ± 0.6	2 ± 1	***<.001*****
Cough Mean ± SD	2.4 + 1	4.3 + 1	<.007**
Retractions Mean ± SD	1.5 ± 0.5	3 ± 1	***<.001*****
Rales Mean ± SD	2.3 ± 1	3.4 ± 1	***<.001*****
Wheezing Mean ± SD	0.6 ± 0.8 (less than a day)	1.3 + 1	***<.001*****
Improvement of Appetite Mean ± SD	1 ± 0.2	2 ± 1	***<.001*****
Hospital stay Mean ± SD	2.4 + 1	4.3 + 1	<.007**
WBC After 3 days	6.7 + 2	7 .6+ 3	.07**

*significant difference if p-value is <.05
*** computed using Chi-square Test, SPSS Version 10
** computed using independent samples T-test

Subgroup Analysis of Patients Without other Adjunct Pharmacologic Intervention

We compared the major outcomes among those who *did not* receive other adjunct medications such as paracetamol, mucolytics, anti-asthmatics, and phenylpropanolamine between the two groups.

Results show that among subjects who received OHHIRA-OMX capsules, the mean days for fever to resolve was statistically shorter than the placebo group. (< 1 day versus 2 days, p-value =.024). Similarly, mean hospital stay and mean day for coughing to resolve were significantly shorter in the OMX group when compared with control. 3 days versus 5 days for both outcomes (both p-values=.007). (See figure1 and 2). Other aforementioned tests did not reach statistical significance.

This goes to show that in patients with community acquired pneumonia, the giving of OMX shortened days of illness.

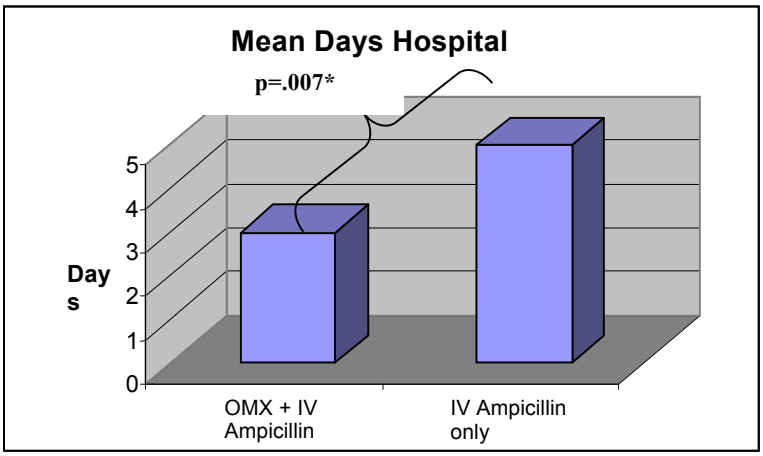


Figure-1 Mean Days Hospital Stay of Children with Pneumonia Receiving OMX with IV Ampicillin vs IV Ampicillin alone, RCT, 2005
*computed using Independent Samples T-test, SPSS 10

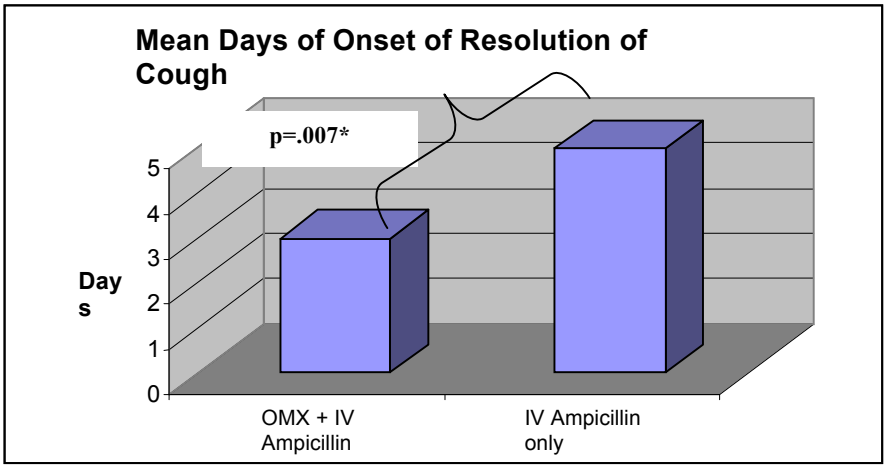


Figure-2 Mean Days of Onset of Resolution of Cough among Children with Pneumonia Receiving OMX with IV Ampicillin vs IV Ampicillin alone, RCT, 2005

*computed using Independent Samples T-test, SPSS 10

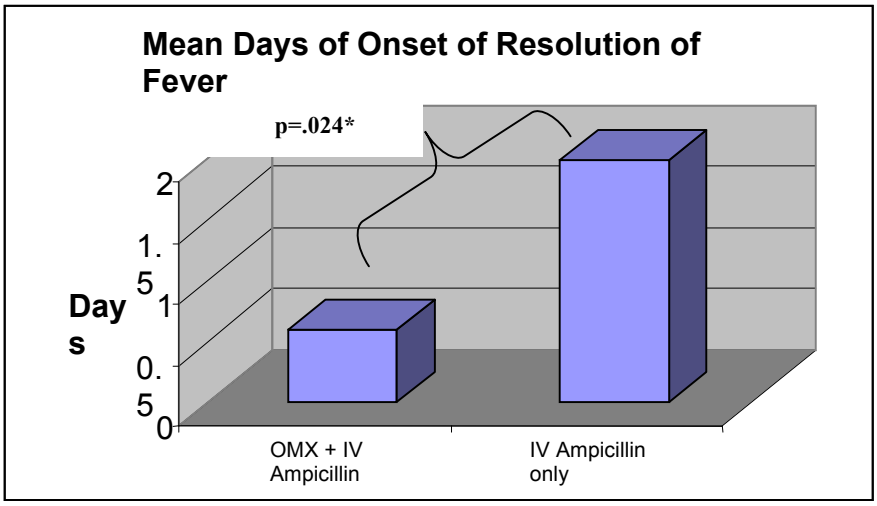


Figure-3 Mean Days of Onset of Resolution of Fever among Children with Pneumonia Receiving OMX with IV Ampicillin vs IV Ampicillin alone, RCT, 2005

*computed using Independent Samples T-test, SPSS 10
*computed using EPI-INFO Stat Calc, 2000

Group	Tachypnea at 3 days	No tachypnea at 3days	Relative Risk*	RRR,ARR, NNT
OHHIRA	**2**	**38**	**RR=0.11**	**RRR= 0.89**
No OHHIRA	**17**	**19**	95% CI .03,0.43 P<.001	**ARR=0.42** **NNT= 2**

Table-8 **Effect Size of OMX Ohhira with Persistence of Tachypnea During the 3rd Day as Outcome**

*computed using EPI-INFO Stat Calc, 2000

We calculated the relative risk of persistent tachypnea up to the 3rd day of illness as the main outcome. Results show that the risk of developing this outcome is 0.11 times in favor of the OHHIRA plus antibiotic versus antibiotic alone. (RR-0.11, 95% CI 0.030, 0.43, p<.001).

Calculating for the relative risk reduction (RRR)

$$RRR = \frac{RT-RC}{RC}$$

0.05-0.47/0.47

RRR=0.89

ARR = RT-RC

where RT = 2/40 = 0.05 NNT = 1/ARR = 1/0.42

where RC = 17/36 = 0.47 NNT=2

ARR = 0.42

Table-9 **Effect Size of OHHIRA Using Chest- X-Ray as Parameter**

Group	Improvement	Worsened	Relative Risk*	RRR,ARR, NNT
OHHIRA	**13**	**1**	**RR=0.07**	**RRR= .0714**
No OHHIRA	**23**	**13**	95% CI .01-0.50 P<.001	**ARR=0.2897** **NNT= 3**

We calculated the relative risk of non-improvement on chest x-ray up to the 3rd day of illness as the main outcome. Results show that the risk of developing this outcome is 0.07 times in favor for the antibiotic alone vs. OHHIRA plus antibiotic (RR-0.07, 95% CI 0.01, 0.50, p<.001).

Shifting of Antibiotics During 3rd day of Treatment

We determined the risk of shifting antibiotics as an indication of *treatment failure* in the experimental arm (OHHIRA). (See contingency Table-10 below)

The risk of shifting antibiotics if one uses OHHIRA as an adjunct therapy is less, RR=.02 (95% CI 0, 0.17, p<.001) in favor of the treatment arm when compared with standard antibiotics (Ampicillin alone).

Table-10 **Shifting Antibiotics During 3rd day of Treatment ("treatment failure")**

Shifting of Antibiotics	**OHHIRA + IV Ampicillin N=40**	**IV Ampicillin Only N=36**	**Relative Risk* 95% CI, p-value**
Yes	1	20	RR= .02 (0,0.17) P=<.001
No	39	16	

*Significant risk if RR is >1, p-value <.05
*computed using Stat Calc, EPI Info 2000

DISCUSSION:

The infants' immature intestinal immune system develops as it comes in contact with dietary and microbial antigens in the gut. Colonization of the gut with appropriate microflora particularly lactobacillus in the small intestine and bifidobacterium in the colon contributes greatly towards the host defense. These are through colonization resistance and interactions with the immune system. [1] In a study done by Gill et al in 2001, oral delivery of live and heat –killed Lactobacillus rhamnosus per day to mice was reported to stimulate the phagocytic activities in the blood and peritoneal leukocytes. However only live microorganisms can enhance gut immunity. Dendritic cells which are found throughout the gut have an important immunoregulatory function especially in relation to T helper cells. In a study done by Christensen et al in 2002, Lactobacilli killed by irradiation were found to stimulate dendritic cell activity with respect to interleukin and TNF- alpha synthesis. Immune function often declines with sickness and extremes of age who are the potential benefactors of probiotic therapy. [2]

According to Fuller in 1992, a good probiotic should be multistrain, highly concentrated, microencapsulated, and has good storage capability. In this study, we utilized OMX capsules which has 12 different strains of lactobacilli and bifidobacterium which is specific to adults (B. bifidum Malyoth) and children (B. bifidum infantis), with 60 million viable bacteria. It also contains 18 essential and non- essential amino acids, Vitamin B- complex (B6, B12, Folic acid, Niacinamide, Panthotenic acid, Biotin, Inositol, Riboflavin, and Thiamine), and minerals (Iron, Calcium, Potassium, Sodium and Phosporus). It is housed in a hard gelatin enteric coated capsule after an entire bacterial mass was freeze-dried making it resistance to the gut acidic environment as it travel. It is stable in reasonable external environment, needs no refrigeration and has shelf life of three years. [3]

The OMX Probiotic capsule is 100 percent natural vegetarian and non- dairy formula. Chemicals, preservatives, artificial additives, coloring agents and animal by- products were never used. Only naturally maturing

organic fertilizers are used in the growing process. Mountain spring water was the only liquid used in this product. In human trial conducted at Okayama University from 1979 to 1991, 1250 subjects were randomly chosen. The following are some of the findings: improved digestive, liver, bowel, circulatory, muscle, joints and sleep functions; decreased yeast and oral cavity infection and strengthened the immune system. Its use in respiratory tract infection such as Pneumonia was believed to be through colonization resistance and interaction with the immune system.

This randomized clinical trial is the first to study the effects of probiotics in infants with severe pneumonia here in the Philippines. Studies done abroad were mostly on diarrheal diseases. There were few published journals and articles regarding its therapeutic use in infants and children. In a study done by Hatakka, et al at Finland in 2001, Lactobacilli rhamnosus enriched milk given once daily for seven months in 594 children aged 1- 6 years old, showed reduced risk of complication of respiratory tract infection such as Otitis and sinusitis (21%), and bronchitis and pneumonia (17%). It also revealed fewer days of absence in school and less likely to require antibiotics.[4]

Our study supported their findings. We have shown that OMX Probiotic as an adjunctive treatment with intravenous Ampicillin in severe pneumonia has significantly reduced the duration of cough and hospital stay, 2.4 days compared to 4.3 days in the control group (p- value of <0.007). The same positive effect was also shown in the resolution of tachypnea and retraction, 1.5 days in the Probiotic group compared 4.3 days in the control (p- value of <0.001). Improvement of the tachypnea and resolution of fever were also significantly reduced in duration, 1 day vs. 2 days in the control group (p- value of <0.001). This study also shown that on the day 3 of the trial, 2 patients (5%) in the Probiotic group compared to 17 patients (47%) were still tachypneic with RR of 0.11, RRR of 0.84, ARR of 0.42 and NNT of 2. RRR of 0.89 mean that the use of Probiotics reduced the risk of Pneumonia by 89% in comparison to the non- probiotic group. The NNT or number needed to treat in this study was 2, meaning we would have to treat only 2 patients with Probiotics to prevent an episode of severe pneumonia. This study further showed that shifting of antibiotics on the 3rd day of treatment was statistically significant because only 1 patient on the treatment group needed to be shifted to IV Cefuroxime compared to 16 patients in the control group (RR 0.02, p= value <0.001).

The use of health supplements was recently increasing, consumers with extra cash to spend did not mind spending a little extra to keep them healthier and recover earlier from illness.

There was no known reported adverse effect in the use of probiotics. In a study done in Malaysia in 2000 by Dr. Ohhira, the acute and sub- acute toxicity of OMX capsule was determined in mice using SGOT, SGPT, and BUN as parameters. It showed no toxicity at all. However in this study, there was one patient who developed generalized pruritic rashes after two doses which disappeared after discontinuation of the drug. But it cannot be directly attributed to the use of OMX capsule hence a bigger sample size could have given us more concise findings and comparisons.

Our study has observed the requirements for a standard randomized controlled trial. The generated power of this study (the ability to reject the false null hypothesis) is computed at 76%. Although the results of this study reached statistical significance, we opt to recommend another study using bigger sample size. The process of sampling randomization has been deemed adequate as evidenced by the homogeneity of samples at baseline.

CONCLUSION

Pneumonia is among the top three leading causes of consultation, admission and death globally. In our study, it showed that probiotics as an adjunctive treatment can significantly shorten the duration of illness and hospital stay and coughing episodes in patients whether they received previously other treatment as antipyretics, mucolytics and decongestants (2.4 days in treatment group vs. 4.3 days in the control group) or not. Observable clinical significance in a shorter mean day of onset of resolution of Tachypnea for age, cough, fever, rales, retractions, wheezing, improvement of appetite or return to usual feeding habits, and shortened hospital stay of OMX is administered with appropriate dosage of rational antibacterials. This can save much time and anxiety to both the patient and the caregiver. Adverse effects are better determined using a larger scale population.

RECOMMENDATION

The authors recommend a placebo controlled trial in a larger population size. They further suggest to determine the proper timing of giving the probiotics in relation to the administration of the antibiotics.

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