CRITICAL REVIEW

ACUTE RESPIRATORY INFECTIONS IN PAKISTAN: HAVE WE MADE ANY PROGRESS?

Tauseef Ahmad Khan, Syed Ali Madni and Anita K.M. Zaidi

ABSTRACT

Acute respiratory infections (ARI) are the leading cause of death in young children in Pakistan, responsible for 20-30% of all child deaths under age 5 years. This paper summarizes the research and technical development efforts over the last 15 years which have contributed to improving the effectiveness of the case management strategy to reduce mortality from pneumonia in children in Pakistan. Community intervention is viable, effective and practical. Rising antimicrobial resistance among commonly used and low-cost oral agents is of significant concern. Appropriate monitoring and evaluation of the impact of the ARI control programme is lacking. Lack of funding for programmatic activities, lack of coordination with other child survival programs, inadequate training for community health workers and general practitioners in the private sector, lack of public awareness about seeking timely and appropriate care, and insufficient planning and support for ARI programmatic activities at provincial and district levels are major hindrances in decreasing the burden of ARI in the country. The recent introduction of the community-based Lady Health Worker (LHW) Programme and WHO and UNICEF-sponsored integrated management of childhood illness initiative present ideal opportunities for re-emphasizing early case detection and appropriate case management of ARI. Ultimately, focusing on preventive strategies such as improving nutrition, reducing indoor pollution, improving mass vaccination, as well as introduction of new vaccines effective against important respiratory pathogens will likely have the most impact on reducing severe ARI and deaths from severe disease.

KEY WORDS: *Acute respiratory infections (ARI). Pneumonia. Bronchiolitis. Antimicrobial resistance. Infant mortality. Immunization. Integrated management of childhood illness.*

INTRODUCTION

Acute respiratory infections (ARI) are now the leading cause of child mortality in the developing world.[1,2] It is estimated that globally at least 4 million children die annually of ARI, with severe lower respiratory disease (bronchiolitis and pneumonia) accounting for most of the deaths.[3] In Pakistan alone an estimated 15 million ARI episodes in children occur annually leading to at least 100,000 child deaths each year, second only to diarrheal disease-related mortality.[4,5]

Acute respiratory infections cover the spectrum of infectious illness of the respiratory tract, ranging from mild upper respiratory infections to serious infections of the lower respiratory tract (bronchiolitis and pneumonia). Upper respiratory infections are most often due to viruses and are rarely life-threatening. On the other hand, lower respiratory infections (severe ARI) can be due to viruses or bacteria, or a combination of the two. Severe ARI are responsible for a great deal of the morbidity and mortality suffered by children in South Asia and as mentioned previously, a leading cause of infant and child mortality in Pakistan.[2]

BURDEN OF DISEASE

Available evidence indicates that the burden of acute ARI in Pakistan is significant. The National Health Survey of Pakistan (1990-1994) found that children under 5 years of age suffer an average of 6 episodes per year of cough with fever.[6] There was little gender and locale variation.

The Pakistan Demographic and Health survey of nearly 6000 children conducted in various households throughout the country during years 1990-1991 showed that 1 in 6 children had suffered from symptoms of ARI (cough and rapid breathing) during the two weeks preceding the survey. Urban areas had lower prevalence as did children whose mothers were more educated.[7] A UNICEF-sponsored Multiple Indicator Cluster Survey in 1995 reported that 37% of children had developed symptoms of ARI in the preceding 2 weeks of whom only 53% had sought appropriate medical attention (Table I).[8]

HOSPITAL DATA: Several hospital-based studies have reported ARI to be one of the major causes of hospitalization (Figure 1). Admissions due to ARI have ranged from 10 to 35%

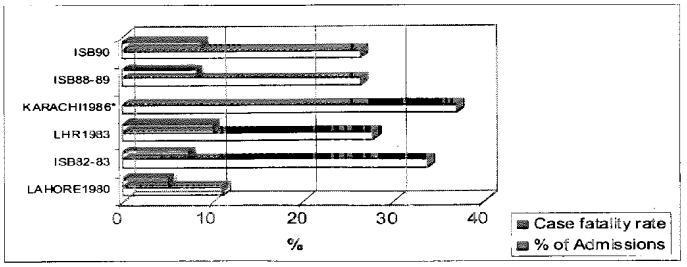


Figure 1: Percentage of hospital admissions due to ARI in different hospitals and case-fatality rates.[9-12]

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and the case-fatality rates between 5-8%.[9-12] In a study by Khan *et al.* in Islamabad, one–third of all pediatric outpatient consultations and 11% of all admissions were due to ARI.[13] In another study done over a period of 3-years (1989-1992) Qazi *et al.* observed that 18 to 26% of all children presenting to the Islamabad Children's Hospital were given a diagnosis of ARI and approximately, 2-5% of ARI are severe enough to require hospitalization and injectable therapy.[14] (Figure 1)

COMMUNITY DATA: Several studies reported causes of childhood mortality from 1980 onwards. [7;15-20] All these studies used verbal autopsies (rather than clinician diagnoses) to estimate the causes of death. Table II shows deaths due to ARI and diarrhea as reported by these studies. The proportion of deaths attributed to ARI ranged from 7.4%-46% in different studies. We would have liked to derive a nationally representative composite figure for the proportion of childhood deaths attributed to ARI in Pakistan but vastly different terminologies used to assign causes of deaths in the studies prevented us from undertaking this exercise. (Table II)

Only the 1990-1991 Pakistan Demographic and Health Survey can be regarded as nationally representative. This survey calculates an ARI-specific mortality of 12% among all causes of under-5 deaths.[7] An interesting observation from this table is the regional variation noted in relation to ARI mortality which appears to be higher in relatively colder climate areas. In an important community-based study from Abbottabad, Khan and colleagues reported severe ARI mortality rate in infants (IMR) as 36.8 per 1000 live births, while total IMR was 96/1000 live births i.e. severe ARI was responsible for over 40% of all infant deaths in this study.[15]

Table I: Prevalence of ARI.

ARI	Pakistan Demographic and Health Survey (1990)[7]	Multiple Indicator Cluster Survey 1995)[8]
ARI in preceding 2 weeks (%)	16	37
ARI needing assessment (%)	16	24
Children with ARI taken to health facility (%)	65	53

RISK FACTORS

Many risk factors underline the development of severe ARI in Pakistani children. These include age less than 1 year, malnutrition, Vitamin A deficiency, low-birth weight, lack of immunization, lack of breast-feeding, crowding, and exposure to indoor pollutants from wood or cow dung combustion or smoking.[21,22] Similar risk factors have been identified in other developing countries.[23-25]

Indoor air pollution, as a risk factor for developing severe ARI deserves special mention. Biomass consumption for household cooking and heating in the absence of adequate ventilation leads to high levels of indoor air pollution including particulate matter which is severely damaging to respiratory tracts.[26-28] Indoor air pollution from wood combustion for heating purposes may be an explanation for higher burdens of respiratory infections in cooler climates of Pakistan. Improved stove design in houses decreases prevalence of ARI as shown by studies done in some developing countries.[29] Outdoor air pollution and exposure to tobacco smoke have also been shown to be important risk factors for ARI in many countries.[30] Exposure to passive tobacco smoke can increase the risk for development of invasive pneumococcal infections in immunocompetent adults by two fold.[31] Similar data for children are not available but because of narrower airways that can easily be obstructed by particulate matter, children probably have an even more dramatic increased risk of invasive pneumococcal disease than adults.

Table II: Causes of death due to diarrhea and respiratory infections among children in Pakistan (in %).

A

Author/ Publication date	Khan MA 1984[17]		Khan SR 1993[16]	Khan AJ 1990[15]	Marsh D 1993[18]	Pakistan Demographic and Health Survey 1990[7]
Area	Karachi		Lahore	Abbottabad[a]	Gilgit	Pakistan
Year	1982		1984-87	1985-87	1988-91	1990-91
Age range	0-12 years	0-1 month	0-2 years	0-5years	0-5 years	0-5 years
Children studied	2536	744	1476	1194	415 Households	7193 Households
Number died	431	201	159	49	66	548
DISEASE(%)						
Diarrhea	38	0	36	22	35	17
ARI	7	10	13	37	44	12[b]
Others	55	90	51	41	21	71

B

Maternal and infant mortality survey 1992-1993[19]

Hazara 1993		Peshawar 1993		DI Khan 1993		Khyber 1993		Kurram 1993		Fikree FF 2002[20] Rural NWFP/Baloch[34] 1990-94	
0-1yr	1-5yr	0-1yr	1-5yr	0-1yr	1-5yr	0-1yr	1-5yr	0-1yr	1-5yr	0-1 month	1-12 months
7732		10315		8128		4506		3667		15360	
236	38	317	70	212	48	173	27	175	33	870	662
DISEASE(%)											
26	50	22	44	31	38	22	41	22	21	5	43
12	16	13	21	9	10	20	33	33	46	6	19
60	34	65	35	60	52	58	26	45	33	89	38

[a] Control Village only [b] Pneumonia=5% + Cough=7%

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ETIOLOGY

The cause of lower respiratory tract disease in children is not easy to confirm microbiologically because of difficulty in obtaining adequate sputum specimens and lack of correlation between upper respiratory tract flora and organisms causing lower respiratory disease.[32] Despite the low yield many hospital based studies conducted in Pakistan have tried to determine the etiology of ALRI in children. *Streptococcus pneumoniae* and *Haemophilus influenzae* are the leading bacterial causes of severe community-acquired acute lower respiratory infections (ALRI) in children.[33] A comprehensive study on the etiology of ALRI was performed by Ghafoor *et al.* in the Rawalpindi/Islamabad area in 1986-1988 (Tables III and IV).

The role of viruses in severe ARI in developing countries has not been fully elucidated. Respiratory tract damage due to pre-existing severe RSV infection probably predisposes towards development of invasive bacterial disease.

ARI CONTROL STRATEGIES

Recognition of the importance of ARI as a leading cause of death among young children globally, led to the development of WHO's ARI Control Strategy in the 1980s.[39] This approach was based on certain facts. Upper respiratory infections are almost always benign and can be managed at home with supportive care only. Many risk factors for severe ARI are difficult or impossible to modify (e.g. age, low-birth weight, malnutrition, indoor pollution). Most deaths from ARI were occurring

Table III: Etiology of bacteremic acute respiratory infections in Pakistan.

Name of investigator	Ghafoor[34]	Naseer[36]	Mastro[35]	Strauss[38]	Saqib[37]
Area	Rawalpindi/Islamabad	Rawalpindi	Rawalpindi/Islamabad	Rawalpindi/Islamabad[a]	Bahawalpur
(year)	(1986 - 88)	1991	(1989 -1990)	(1991-1992)	(1998)
Number of patients	1047	61	601	595	50
Specimen type	Blood cultures	Empyema (pleural fluid) cultures	Blood cultures	Blood cultures	Empyema (pleural fluid cultures)
Percentage with positive cultures	33%	64%	36%	22%	80%
Organisms isolated (%)					
Pneumococcus	11.6	18	18	13.6	
Haemophilus influenzae b	7.35	5[b]	3.3	0.6	
H. influenzae non-type b	4.5		16.6	7.8	
Staphylococcus aureus	2.4	39.3	0.2		68
Klebsiella pneumoniae	4.4				
Others	2.67	21.3	1.2		12
No growth (negative culture)	67	36[c]	64	78	20

a: Only reported isolation of pneumococcus and *H. influenzae*
b: *Haemophilus influenzae* not serotyped into type b or non-type b
c: Adds up to more than 100% because some cultures grew more than 1 type of pathogen

Table IV: Viral etiology of severe acute respiratory infections.

Name of investigator Area (year)	Ghafoor[34] Rawalpindi/Islamabad (1986-88)					
Number of patients (total 1492)						
Age range in months	0-1	2-5	6-11	12-23	24-60	< 60 total
Organisms isolated (%)[a]						
RSV	9	154	108	91	129	491
Parainfluenza 1,2,3	0	2	1	4	6	13
Influenza A	0	1	3	2	3	10
Influenza B	0	2	3	0	5	10
Adenovirus	2	4	5	9	9	29
No virus detected	19	158	199	239	324	939
Total specimens	30	321	320	345	476	1492

a: 126 (26%) of 491 infections due to RSV also had bacteremia due to *H .influenzae* (65 cases) or *S. pneumoniae* (61 cases). There was an associated viral infection in 53% of children with *Haemophilus* bacteremia and in 47% of those with pneumococcal bacteremia.

Pneumococci and *H. influenzae* were found to be common bacterial pathogens and respiratory syncitial virus (RSV) was the most frequently isolated viral agent.[34] Of note, ARI due to RSV infection frequently co-existed with bacterial pneumonia. Several other studies have also reported the etiology of pneumonia, mainly from the Rawalpindi/Islamabad area.(Table III).[35-38] All have found pneumococci and *H. influenzae* to be common agents. However, studies reporting pleural fluid cultures in pneumonia complicated by empyema have reported a high predominance of *Staphylococcus aureus*.[36,37]

in areas with minimal health care and diagnostic facilities. Delays in seeking health or inaccessibility of health care were responsible for a large number of deaths.

The approach advocated called for decreasing child mortality from pneumonia by developing simple algorithms for early recognition and management of ARI according to degree of severity, which could be used by health care providers at first level facilities. Appropriate guidelines for management of severe pneumonia in hospital settings were also developed.[40]

The recommendations called for classifying children younger than 5 years of age with respiratory signs and symptoms into upper respiratory disease (requiring no treatment), and lower respiratory disease based on the presence of tachypnea. Children without chest indrawing or danger sings could be managed as outpatients with an antimicrobial agent (co-trimoxazole, procaine, penicillin, ampicillin or amoxicillin). Children with chest indrawing or other danger signs needed referral to a medical facility for treatment with a parenteral antimicrobial agent (benzylpenicillin, ampicillin, chloramphenicol, gentamicin, or cloxacillin) and supportive care.[40] (Table V).

The WHO ARI approach identified children with lower respiratory infection with a sensitivity and specificity of about 80%.[39] Auscultation and chest radiography are not routinely employed.

PAKISTAN'S NATIONAL ARI PROGRAMME

Pakistan adopted the ARI standardized case management

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Table V: The ARI case management protocol.

Does child have cough or difficult breathing?
If yes,

Ask:
For how long?
Look, listen
- Count the breathe for one minute.
- Look for chest indrawing.
- Look and listen for stridor.
- Look and listen for wheeze.

if child is:
- 2 months upto 12 months
- 12 moths upto 5 years

Fast breathing is:
- 50 breeathis per minute or more
- 40 breaths per minute or more

Classify cough or difficult breathing.

Sings	Classify as	Treatment
Any general danger sign or Stridor in calm child or Chest indrawing	Severe pneumonia or very severe disease	- Give first dose of appropriate antibiotic. - Treat wheezing if present. - Treat the child to prevent low blood sugar. - Refer urgently to hospital.
Fast breathing	Pneumonia	- Give and contrimoxazole for 5 days. - Treat wheezing if present. - Soothe the throat and relieve the cough with a safe remedy. - Advise mother when to return immediately. - Follow-up in 2 days.
No signs of pneumonia or very severe disease	No pneumonia cough or cold	- Treat wheezing if present. - If coughing more than 30 days, refer for assessment. - Soothe the throat and relieve the cough with a safe remedy. - Advise mother when to return immediately. - Follow-up in 2 days if wheezing.

Source: Integrated Management of Childhood Diseases, Government of Pakistan. 2001

approach and launched the National ARI Control Programme in 1989.[13] The objectives of the programme were to reduce the severity of and mortality from pneumonia in children; to reduce the incidence of acute lower respiratory infections (ALRI); to reduce the severity of and complications from acute upper respiratory infection; to rationalize the use of antimicrobial and other drugs for the treatment of ARI in children.

The control strategies to achieve these objectives were as follows:

1. PROPER CASE MANAGEMENT: It was demonstrated by several studies that children who die from pneumonia are frequently treated inappropriately, brought too late for treatment, or not treated at all.
2. IMMUNIZATION: is a specific strategy to prevent respiratory infections in children caused by diphtheria, measles, pertussis and tuberculosis.

A large number of multidisciplinary research studies were commissioned in developing countries to test the feasibility as well as impact of a standardized case-management based approach for control of mortality related to ARI.[39] Pakistan's National ARI Control Programme has played a leading role in conducting research related to management of ARI with implications for Pakistan as well as other developing countries. Much knowledge has been amassed as a result of several well-designed studies.[41]

Several hospital and community based studies in Pakistan have observed the successful adoption and implementation of National ARI Programme guidelines to reduce child morbidity and mortality due to ARI.[14 15,35,38,42-45] All these studies were conducted at hospitals or clinics set up within a community, where physicians and community health workers (CHW) trained according to the National ARI Programme guidelines, dispensed medical care to the patients.

The pioneering interventional study performed by Khan *et al.* showed that case management of acute respiratory infection by village-level community health workers backed up by local health centre staff significantly reduced both ALRI-specific mortality rates (by 55%) and the overall child mortality rates (by 29%).[15]

A hospital based study showed that the use of antibiotics in the outpatient department fell from 54.6% to 22.9% and case-fatality rate of children admitted with ARI decreased to 4.9% from a baseline of 9.9%. These results from a tertiary care hospital showed that standard ARI case-management resulted in both reduced antibiotic use and expenditure on drugs.[14]

The above studies and others done in Pakistan and other developing countries have consistently shown that strict application of standard ARI case management guidelines by trained physicians and paramedical staff results in reduced ALRI specific mortality in both hospital and community settings.[14,15,35,38,42-45]

TREATMENT OF ARI IN PAKISTAN

The ARI Control Programme includes outpatient and inpatient management protocols that recommend use of antimicrobial drugs for children with pneumonia.[40] However, little was known about antimicrobial susceptibility of different microbes in most countries where these programmes were being established. Knowledge of antimicrobial susceptibility was considered helpful in guiding the choice of therapeutic agent for optimum efficacy of ARI control programmes. Pakistan was one of the sites for the US National Research Council Board on Science and Technology for International Development's (BOSTID) multi-center collaborative project to define the etiology and epidemiology of ARI in twelve developing counties.[46,47]

ARI trials conducted in Pakistan in the last decade have contributed significantly in optimizing management of uncomplicated pneumonia.(Table VI) Pakistan's National ARI Control Programme recommends co-trimoxazole as the drug of first choice in outpatient management of children with

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Table VI: ARI trials on children 2-59 months old.

Author	Khan[43]		Straus[38]		Hamid[42]	Rasmussen[59]	Rasmussen[44]		Qazi[49]		Qazi[48]	
Area	Islamabad		RWP/ISB		Islamabad	Gilgit	Pakistan		MC		MC	
Year	1991		1991-92		1992-93	1992-93	1995-1996		1998-1999		1998-99	
Setting	Community		Hospital		Hospital	Community	OPD and Community		OPD		OPD	
Criteria	N.S. Pn	N.S.Pn	S.Pn		6 N.S. 77 S; 17 V.S Pn	N.S.Pn	N.S.Pn		N.S.Pn		N.S.Pn	
Type of study	Open study	Double blind R.C.T			Open study	Open study	Double blind R.C.T		Double blind R.P.C.T		Randomized controlled clinical trial	
Number of children	95	98	195	99	203	100	327		1040		980	973	730	741
Therapy	Co-trimox	5 day Amox	5 day Co-trimox	5 day Amox	5 day Co-trimox	Parenteral Amp[a]	Co-trimox	Co-trimox[b]	Co-trimox x2 dose[c]		3Day Amox	5 day Amox	5 day Amox	5 day Co-trimox
Cure rate(%)	91.6	88	87	82	67	89	91.2	80.8	79.4		79	80	83.9	81.1
Failure(%)	8.4	12	13	18	33	11	8.8	19.2	20.6		21	20	16.1	18.9
Interpretation	For severe, life-threatening pneumonia co-trimox is less likely than amoxicillin to be effective						No significant difference				No significant difference		Equally effective	

a: Parenteral ampicillin for severe pneumonia patients and parenteral chloramphenicol for very severe patients.
b: Trimethoprim dose 4mg/kg
c: Trimethoprim dose 8 mg/kg
Co-trimox = Cotrimoxazole, Amox= Amoxicillin
M.C: Multiple cities
S: Sever
S.Pn: Severe pneumnia
N.S.Pn: Non severe pneumonia
V.S.Pn: very severe pneumoonia
R.C.T: Randoimzed controlled trial

non-severe pneumonia because of its low cost, broad-spectrum of activity, and convenient twice-daily dosage schedule. In several studies cotrimoxazole and amoxicillin were shown to be equally effective in the treatment of non-severe pneumonia.[14,38,44,48] However, a recent study by Straus *et al.* found an appreciable failure rate (33%) associated with use of oral cotrimoxazole for severe pneumonia indicating that it should be used with caution in cases of severe pneumonia and only when other alternatives are not available.[38]

Two recent multi-centre trials of short-course therapy for outpatient management of non-severe pneumonia in India and Pakistan have shown that 3 day amoxicillin are as effective as a 5 day regimens with cure rates of approximately 80%.[49,50]

ISSUES WITH PAKISTAN'S NATIONAL ARI CONTROL PROGRAMME

Despite impressive research contributions, there have been problems with implementation of the ARI control programme at a national level and estimates of impact at the national level in reducing ARI specific child mortality or reaching its stated objectives are not available.[5] A few studies that have been conducted to review its progress at a national level have been at best restricted to evaluating a single component or aspect of the programme. Examples of such surveys are the Pakistan Demographic and Health Survey (1990-1991) and Multiple Indicator Cluster Survey of Pakistan (1995) which have made vital information on ARI incidence and mortality available.[7,8] However, more recent data are not available. In the absence of such regular evaluation of impact, it is difficult to discover deficiencies in the programme and keep it relevant and evidence-based to effectively achieve desired objectives. A focused programme review of the ARI control programme was undertaken in 1997 with the help of UNICEF and WHO. Serious lack of funding for programmatic activities, lack of coordination with other child survival programs, inadequate training for lady health workers and general practitioners in the private sector, ineffective monitoring systems to evaluate impact of training, lack of mass public health awareness about seeking timely care, and insufficient planning and support for ARI programmatic activities at provincial and district levels were identified as major deficiencies.[51] Several concrete solutions were proposed but unfortunately, the most recent annual report of the Director General Health reports that the programme received minimal funding in 2000-2001, which severely impacted implementation activities. The ARI programme is currently largely dependent on WHO for survival. Integration with the national integrated management of childhood illness (IMCI) programme is projected to take at least five years.[52]

GENERAL PRACTITIONERS ROLE: A major obstacle in nation-wide implementation of ARI management guidelines may be that the majority of health care activity in Pakistan occurs outside the public sector,[6] whereas training activities of national WHO-sponsored programs are limited to governmental staff and facilities. Studies of health facility utilization patterns in the country have shown that self-employed general practitioners working in the community see and treat the largest proportion of ARI patients.[13,53,54] This ground reality indicates the necessity of involving the private sector health providers in any national child survival programme. Despite several workshops held to increase awareness of general practitioners about recommended ARI case management guidelines the present situation is still far from satisfactory.[55]

ANTIMICROBIAL USE AND THE PROBLEM OF DRUG RESISTANCE: Significant levels of antimicrobial resistance to cotrimoxazole among respiratory pathogens in Pakistan was noted in the early 1990's-only a couple of years after launch of the national ARI programme.[56] Reports of high *in vitro* antimicrobial resistance of *S. pneumoniae* and *H. influenzae* to co-trimoxazole has prompted the programme to reevaluate its treatment policy. Country-wide surveillance from 1991 to 1994 revealed 80% *in vitro* resistance to co-trimoxazole among *S. pneumoniae* isolates and 60% among *H. influenzae* isolates while resistance to amoxicillin was low (Tables VII and VIII).[35,38,46,56,57] The *in vivo* cure rates in

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Table VII: Sequential antibiotic resistance of *Haemophilus influenzae* isolated from blood.

Author Year of study	Weinberg[46,57] 1986-1988	Mastro[35] 1989-1990	Strauss[38] 1991-1992	Tanwani[56] 1991-92	Tanwani[56] 1993-94	AKU[58] 2002a
Location	RWP/ISB	RWP	RWP/ISB	ISB	ISB	KHI
Number with LRTI	1216	601	595	NA	NA	NA
No. of *Haemophilus influenzae* isolates	130	89	81	525	215	NA
Haemophilus type b isolates	64%	3%	7%	NA	NA	NA
Haemophilus Non-type b isolates	36%	92%	93%	NA	NA	NA
Resistance patterns (%)						
Cotrimoxazole	11	42.7	52	61	59.5	79
Ampicillin	7	3.4	0	2.6	1.4	8
Erythromycin	8.6	16.9	NA	NA	NA	NA
Chloramphenicol	0	0	NA	5.7	3.7	5

NA= Not available; RWP = Rawalpindi; ISB = Islamabad; KHI = Karachi
a: Susceptibility results for all isolates received from July- December 2002.
Modified from Bhutta ZA. Burden of *Haemophilus influenzae* and *Streptococcus pneumoniae* infections during childhood in Pakistan. *J Coll Physicians Surg Pak* 2000; 10(9): 346-54.[4]

Table VIII: Sequential antibiotic resistance of *Haemophilus influenzae* isolated from blood.

Author	Mastro[35]	Strauss[38]	Tanwani[56]	Tanwani[56]	AKU[58]
Year of study	1989-1990	1991-1992	1991-92	1993-94	2002[a]
Location	RWP	RWP/ISB	ISB	ISB	KHI
Number with LRTI	601	595	NA	NA	NA
Streptococcus pneumoniae	70	50	718	229	NA
Resistance patterns (%)					
Cotrimoxazole	77.8	66	78.3	79.9	NA
Amoxicillin(A) / Penicillin(P)	11.1 (P)	23 (A)[b]	27.3 (P)[c]	51.5 (P)[c]	1
Chloramphenicol	35.7	NA	15.2	17.5	12
Erythromycin	1.4	NA	NA	NA	22

NA: Not available; RWP = Rawalpindi; ISB = Islamabad; KHI = Karachi
a: Susceptibility results for all isolates received from July- Dec 2002.
b: These were of intermediate susceptibility with a break point of 0.12 µg/µL.
c: Penicillin MIC ≥0.12 µg/mL were reported as resistant by Tanwani. Many of these isolated may have been of intermediate susceptibility explaining the discrepancy observed between these results and susceptibility reported by others.

children with pneumonia treated with cotrimoxazole and amoxicillin have decreased by 7 to 10% since 1989 to approximately 70-80% in recent studies.[38,42-44 48,49,58] The clinical significance of the finding of increased resistance rates in the management of non-severe pneumonia is unknown and Pakistan's ARI control programme and the new integrated management of childhood illnesses (IMCI) algorithms continue to recommend cotrimoxazole as the agent of choice for non-severe pneumonia. Given the appreciable failure rates associated with use of cotrimoxazole for treatment of severe pneumonia, alternative agents such as parenteral ampicillin should be used as first-line therapy.

The drug-related costs of switching to oral amoxicillin for the management of non-severe pneumonia in the out-patient setting have been estimated to be $25 million annually.[41,59] The costs may however, be lower for 3-day amoxicillin regimens.[49,50] At best, switching to amoxicillin as a first-line agent for the out-patient management of non-severe pneumonia would be of short-term utility, given the increasing prevalence of penicillin (amoxicillin) resistance among *S. pneumoniae* and *H. influenzae* in neighbouring countries. Clearly, alternative strategies should focus on decreasing the incidence of severe ARI, such as improving nutrition, vaccination, and environmental conditions as well as introducing newer vaccines effective against respiratory pathogens. The importance of integration with other child health survival programmes like IMCI must again be stressed.

HEALTHCARE SEEKING BEHAVIOUR: The ARI control strategy depends upon early detection of cases. Passive case finding relies upon the mothers' ability to recognize signs of serious ARI disease (fast breathing and chest retractions) and to seek care when such symptoms are noted. In India Bang *et al.* reported that the pneumonia case fatality rate was 0.8% in villages where a major health education initiative had taken place versus 13.5% in control villages.[60] A number of studies in different areas of Pakistan have demonstrated that mothers have inadequate knowledge about danger signs of serious ARI disease in children.[61-63] Delays of care seeking of up to 3-4 days have been noted. The delays are due to factors such as poverty, difficulty in accessing health facilities, lack of time to access medical care, unavailability of staff at governmental health facilities, lack of transportation, limited female autonomy, and caretaker's inability to recognize the seriousness of the child's condition. The nation-wide multiple indicator cluster survey in 1995 revealed that only 11% of mothers mentioned "fast breathing", 9 % mentioned difficulty in breathing, and 3% "chest indrawing" as danger signs of pneumonia.[8] Only 53% of mothers had sought help from appropriate sources after a child suffered from an ARI requiring assessment. This indicates a strong need to improve public awareness about early recognition and timely seeking of care for children with serious respiratory disease.

PREVENTION OF SEVERE ARI INFECTIONS

Although the standardized ARI case-management approach has undoubtedly saved many thousands of lives in the developing world, it can justifiably be criticized for failing to address some major underlying risk factors for severe pneumonia –namely malnutrition, poor housing and indoor air pollution.[13,34]

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PROMOTION OF EXCLUSIVE BREAST FEEDING: Much evidence exists for the protective effects of breastfeeding against infant and child morbidity and mortality, including ARI-related morbidity and mortality.[64] A recent pooled analysis from 8 countries including Pakistan showed that protection against infectious diseases continued well into the second year of life.[65] The protection against ARI may be related to enhanced mucosal immunity as well as preventing diarrhea and malnutrition-related immuno-compromise. As such, promotion of breastfeeding is a simple and effective ARI prevention strategy. However, many descriptive studies in Pakistan have shown that exclusive breastfeeding is only practiced by a minority of mothers.[66,67] While some attention has been given to the promotion of breastfeeding by initiatives such as the Baby Friendly Hospital Initiative and the National Breastfeeding Programme, clearly more needs to be done to promote breastfeeding at the community level. The current governmental programme of Lady Health Workers (LHW Programme) and the WHO-sponsored integrated management of childhood illness (IMCI) initiative present ideal opportunities for doing so.

VITAMIN A AND ZINC SUPPLEMENTATION: Both zinc and vitamin A deficiencies are important underlying risk factors for death due to infectious diseases including ARI.[2] Vitamin A deficiency is associated with increased severity of ARI and supplementation has been shown to reduce mortality rates in young children. Vitamin A deficiency is common in Pakistani children. Pakistan is categorized under the severe subclinical deficiency group of countries by WHO and UNICEF.[68] In children surveyed in Karachi, 16-42% had low levels of vitamin A, and 2% were severely deficient. However, regional variations may exist. Mass supplementation with vitamin A was initiated in Pakistan in 1999.[69] Long-term studies are needed to evaluate if periodic massive doses of vitamin A reduce childhood mortality in Pakistani children. Some have advocated limiting mass supplementation to areas where the majority of children are proven to be vitamin A deficient because of concern about adverse effects associated with excessive levels of vitamin A.

Zinc deficiency increases the risk of mortality from diarrhoea, pneumonia, and malaria by 13–21%.[70] Zinc supplementation may play an important role in prevention and management of ARI but further studies are needed to explore this aspect.

VACCINATION: In addition to standard case management, vaccines have a great potential for reducing childhood deaths. Immunization against measles and pertussis contributes to the prevention of more than one million childhood deaths. New conjugate vaccines against *Haemophilus influenzae* type b have been estimated to have the potential to reduce acute lower respiratory infection (ALRI) deaths by 4%.[71] Substantial reduction may also be obtained by use of a conjugate vaccine effective against the pneumococcal serotypes prevalent in developing countries. An effective vaccine against RSV could also prevent a significant proportion of ALRI deaths.

H. influenzae type b (Hib) and 7-valent pneumococcal conjugate vaccines are now part of routine childhood immunizations in industrialized countries. Hib vaccine has also been introduced in many developing countries. However, cost issues and absence of burden of disease data on invasive Hib disease has precluded introduction in many resource-limited countries. Hib is notoriously difficult to culture, which has resulted in under-estimation of its importance as a cause of childhood pneumonia. However, a Hib vaccine trial in the Gambia demonstrated a 20% reduction in radiologically-proven pneumonia in the group that received Hib vaccine.[72] Whether Hib are an important cause of pneumonia in Pakistan is an unresolved question. Therefore, the question of whether introduction of Hib vaccine in Pakistan's EPI Programme would significantly impact the incidence of pneumonia cannot be answered until further studies have been done to clarify the role of Hib in causing invasive disease in Pakistani children.

Use of the pneumococcal conjugate vaccine is also precluded by lack of adequate knowledge about prevailing serotypes causing invasive disease in Pakistan. The currently licensed vaccine contains serotypes prevalent in industrialized countries. High cost of the vaccine is also a significant limiting factor. Cheaper vaccines containing the serotypes prevalent in developing countries are urgently needed.

CONCLUSION

ARI is the leading cause of death in young children in Pakistan. Community intervention studies provided strong evidence that the strategy is viable, effective and practical in producing a substantial impact on reduction in pneumonia mortality.

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