INTRODUCTION

Controlling acute respiratory infection (ART) becomes increasingly important for Pakistan as oral rehydration therapy lessens mortality from childhood diarrhoea. This paper first reviews the pertinent global and then the Pakistani situation in terms of epidemiology, intervention trials and other significant studies. The case management strategies outlined in the National ART Control Programme are neither complete nor perfect, but they are a thoughtful, urgently needed first step. ART is a major killer of children in the developing world. WHO and UNICEF estimate that over 4 million (30%) of the 14 million under five death annually are due to ART, including measles (1.5 million) and whooping cough (0.5 million). Child health advocates liken this mortality to “one jumbojetful” of coughing, dyspneic children crashing every 45 minutes with no survivors. Acute respiratory infection is the term generally adopted to include both upper ("URI" or “AUTH”) and lower (“LRI" "LRTI" OR "ALRI") respiratory infections that last 2 weeks or less. Upper respiratory infections include conditions above the epiglottis (usually the common cold, tonsillitis, otitis, sinusitis, conjunctivitis and combinations). Lower respiratory infections include epiglottitis, laryngitis, bronchitis, bronchiolitis, broncho-pneumonia, pneumonia and less common conditions like lung abscess and empyema. When ART is used in the primary health care (P1-IC) programmatic sense, it usually targets children under five and focuses on prevention and treatment of lower respiratory infections, especially pneumonia. Pneumonia accounts for 70% of ARI deaths, measles and pertussis for 25% and croup or respiratory syncytial virus (RSV) disease (presumably bronchiolitis) for 5%. National programmes, including Pakistan’s, may also address reducing the morbidity due to upper respiratory infections, mainly otitis, streptococcal tonsillopharyngitis and mastoiditis. When used in this paper, ART will refer to the lower respiratory tract infections and is synonymous with ALRI, the less commonly used term.

GLOBAL ARI SITUATION

Two recent large monographs provide detailed overviews of the global ART situation and control programmes. Other excellent review articles supplement this information. Douglas presents the history of ARE mortality from the pre-antibiotic era to the present. Useful background for any risk factor assessment in developing countries. The WHO case management algorithms based on the key findings of Shann et al in Papua New Guinea have gained a measure of acceptance world-wide. The criteria continue to be refined and reviewed and they form the basis for most large-scale interventions.

Epidemiology of ARI

The Reviews of Infectious Disease monograph summarizes the findings of the Bureau of Science and Technology in Development (BOSTID) epidemiologic studies in 12 developing countries (including Pakistan) between 1983 and 1988:
1. URI incidence rate: overall 6-8 episodes/year; children experienced URI symptoms on the average for 22-40% of a calendar year; but 5-20% of children had no episodes at all.
2. LRI incidence rate: 0.2-4 episodes/year; children spent 0.3- 14% of the time with LRI symptoms.
3. The case fatality ratio (CFR) of LRI was 3-16% (30 + times greater than in developed countries); the
highest being in infants and girls.
4. There was a striking decrease in incidence with age except for a peak at 6-12 months.
5. Males were highly represented, but this may reflect gender preference in health seeking behaviour in
facility-based studies.
6. Peak LRI incidence did not necessarily coincide with the peak URI season. There was little expected
clustering by geography, altitude, climate, rainfall or temperature.
7. Viral pathogens were recoverable in 14-64% of LRI, with RSV responsible for 11-37% of all LRI
and the vast majority of viral LItI.
8. Bacterial pathogens were recoverable in 5-40% of LRI. with pneumococcus as the main causative
bacterium.

There were some differences among the studies. For example, Bangladesh had little severe
bronchiolitis and H. influenzae disease. Pakistan, on the other hand, had much H. influenzae disease,
including non-typable strains. Whether different handling of these fastidious organisms accounted for
the divergent findings is not known.

In addition to the above data, further identification of risk factors was remarkably unrewarding perhaps
because of study design. That is, maternal education had very little erect when dichotomized between
primary and secondary schooling. Crowding and sharing sleeping quarters had a variable effect; but no
measure of crowded day-time activities (as in day care centres or creches) was made. Household
tobacco smoking also had a variable effect. Maternal age had a inconsistent effect possibly because the
inexperience of a youthful mother was balanced by fewer children. In summary, country risk profiles
varied, possibly due to true differences and study design limitations. A 1989 workshop report from
John Hopkins University summarized laboratory and field experience in attempting to understand and
control childhood ART in developing countries. It highlighted the most important risk factors:
malnutrition (including vitamin A deficiency and lack of breast feeding), low birth weight,
overcrowding and indoor air pollution. Added to this was early infancy with its especially high case
fatality ratio. Understudied, but certainly important, were cultural factors which delayed or prevented
life-saving treatment with antibiotics or resulted in harmful measures.

**Community intervention trials**

Of ART community intervention trials reported in literature, 4 are of particular interest because of their
local implications, one each in India, Nepal, Bangladesh and Pakistan. They are summarized in the
Table.
Bang et al. undertook a 102 village (58 for intervention and 44 for concurrent comparison) study in Gadchiroli, Maharashtra, India, to investigate the usefulness of passive case finding, massive health education and case-management strategies to lower cause-specific childhood mortality in the absence of other child survival interventions. Key design features included: (1) using traditional birth attendants (TBAs) in addition to government village health workers (VUWs) and paramedics to improve overall coverage, especially of neonates; (2) employing the visual impression of "tachypnea" since TBAs could not count up to 50; (3) otherwise employing the initial WHO criteria of cough and rapid breathing to diagnose pneumonia; (4) referring to co-trimoxazole as "kotra" to identify it as special for pneumonia; (5) using a careful verbal autopsy method; (6) conducting a concurrent morbidity study in 40% of the villages wherein each household was visited every 2 weeks.

The simplicity and clarity of their four health education messages bear repeating:
1. Cough in child without fast breathing or difficulty in breathing is simple and can be managed at home without special medicines.
2. Fast breathing and/or difficulty in breathing may indicate pneumonia, which is life-threatening.
3. Treatment for pneumonia is available in your village with the paramedic, VT-iW or TBA (their names were announced).
4. The medicine is called "kotra" (for co-trimoxazole) which is effective, safe and available free.

The results were impressive. The morbidity survey found an attack rate of 6.47 episodes of TJSR and 0.13 episodes of pneumonia per child per year in both intervention and control villages. The CFR in the intervention villages was 0.8% compared to 13.5% in the control villages. They reported that 77% of the difference in total mortality among children under 5 years (40.7 vs 28.5 per 1000 = 12.2/1000) was due to a lower ART-specific mortality. The cost of co-trimoxazole was 2.47 cents (US) per child aged 0-4 years in the intervention area, 25 cents per pneumonia case treated and US$2.64 per pneumonia death prevented. This did not take into account the cost of the whole programme, of course. However, the authors have demonstrated the economic practicability of employing community health education and TBAs (who are often out of the mainstream of PHC activities) as effective providers of clinical care in controlling potentially life-threatening illness. Another study from Nepal by Pandey et al. had similarities to the Bang study reviewed above. The study population was large, encompassing over
6600 children under five. The providers were community health workers (CHWs) who used WHO guidelines with cotrimoxazole as the first-line treatment. Other key design features included: (1) active case detection with household visits every 2 weeks; (2) progressive phase-in with each sub-district acting as its own comparison over time; (3) battery-operated beeping timer devised due to absence of wrist-watches; (4) absence of alternative care in this remote, unserved population; (5) absence of other PHC interventions as the CHWs were only trained in AM case management and (6) conservative analysis on the basis of intention to treat. The results again were impressive: over three years of treatment there was a 28% reduction in overall childhood mortality. This included mortality reductions for pneumonia of 30%, for diarrhoea (alone or in combination with pneumonia) 36% and for measles 90%. ART was implicated as contributing to much non-AM child mortality, probably through serious morbidity and associated nutritional compromise. Of special importance was the rapid course of the disease in children who died - especially young infants whose course averaged 4 days of tachypnea and 3.7 days of intercostal retraction. Thus, even fortnightly active case finding failed to identify many ill children prior to death. A more recent community intervention study from Matlab, Bangladesh is the first report measuring the impact of adding an AM component to a nearly complete range of existing PHC services. Design features included an adjacent concurrent control population of 100,000 which received only government health services and a test population, also of 100,000, which had been receiving PHC services for over two years to which was added active and passive ART case detection and treatment by CHWs according to WHO guidelines. Cause-specific mortality analysis was based on assignment of cause of death of children from age 1 to 60 months based on the clinical judgement of medically trained personnel; formal verbal autopsy algorithms were not used. Their findings were consistent with the two previous studies although their baseline mortality figures were more favourable. This likely reflected the benefit of pre-existing PHC services in the test population, the ‘spill-over’ of these effects in the comparison communities served by government services and secular trends in both. ARI-specific mortality at baseline was 28% less in PHC than government served areas; after two years of the intervention, cause-specific mortality was decreased a further 32% in the intervention area but remained unchanged in the comparison area. The reduction in AM-specific mortality accounted for 30% of the overall reduction in under five mortality rate (per 1000 child-year of exposure) in the intervention group. The study concluded that indirect effects of PHC services (such as measles vaccination, promotion of breast feeding and birth-spacing) and direct effects of AM control programmes additively reduced ART-specific and overall child mortality.

Other studies
A host of related aspects needs further study. UNICEF outlines four types of research: case management (or clinical), behavioural, health system and disease prevention. To date, however, there is a paucity of data addressing the last three. From Bangladesh comes a report of an anthropological focus group study which described beliefs and practices of poor rural and urban mothers and grandmothers. As a basis for discussion the investigators showed the UNICEF AM training film (demonstrating children with and without various respiratory signs) to small groups of women. Some of the major findings were: (1) women recognized difficult (but not rapid) breathing as dangerous; (2) they believed that AM was due to physical cold (weather, breast milk from “chilled” mother); (3) traditional treatments were both useful (protecting from chills) and harmful (dietary restriction); (4) they believed neonatal AM was mild and/or supernaturally caused and that boys were more susceptible to AM than girls and (5) family, rather than individual, decision-making was employed for seeking treatment. In a very different study, Rahman et al studied the co-infections of simultaneous AM and diarrhoea in Dhaka. This pneumonia-diarrhoea complex is commonly seen by those performing mortality reviews in the developing world. The authors considered 401 children under five hospitalized in Matlab for acute lower respiratory tract infections and diarrhoea. They identified respiratory pathogens in 30%, diarrhoeal pathogens in 34%, both in 12% and neither in 48%. Symptoms developed within 2 days of
each other in 53% of cases; ART symptoms preceded GI symptoms in 32% and followed in 15%.
Although the incidence of co-infection in the general population cannot be estimated from this facility-based study, evidence is provided to confirm that bonafide co-infections are not uncommon.

**ARI SITUATION IN PAKISTAN**

Pakistan has an estimated 80,000 child death annually attributed to AM and an additional 170,000 due to measles²¹. Risk factors are widely prevalent, but little studied. Recent and on-going research holds promise for guiding national policy and contributing to world-wide ARI control. Indeed, at the December 1990 National Workshop on Policy Related Research - Action Plan for the Nineties, organized by the Ministry of Health, the Ministry of Planning and Development and the Aga Khan University (AKU), AR! was ranked sixth of fifteen priority areas for national policy-linked research with a call for increasing research capacity in the near-term.

**Epidemiology of ARI**

Pakistan data are imperfect, yet the picture is consistent with the developing world in general in that AR! is a major cause of morbidity and mortality. Morbidity in the northern areas has been reviewed in 1989 by Rasmussen and Zaidi (unpublished). They found that respiratory complaints accounted for 27% of all outpatient visits to Gilgit District Headquarter Hospital, all peripheral Government Civil Hospitals, Civil Dispensaries and First Aid Posts and the 19 Aga Khan Health Services Maternal and Child Health Centres. Two percent of the 29% was due to pneumonia, 4% bronchitis, 6% asthma. During the winter (November-April) 46% of OPD visits at a Gilgit facility were due to ARI. Facility-based information from the five AKU-led Primary Health Care sites in 1990 (unpublished) underscored the large community burden of ARI in settings of urban poverty. Of all visits for all ages, 20% were for URI, 4% for ear problems, 2% for LRTI and 2% for asthma. Northern areas mortality was measured in a 1986 Aga Khan University unpublished demographic and health survey of 2289 households. Respiratory diseases accounted for 8% of all mortality. In a Government of Pakistan qualitative assessment of health officials in Northern Areas and Chitral²² doctors attributed 18-20% of infant deaths to pneumonia. The child specialist at the Gilgit 1)istrict Headquarters Hospital recorded his 1989 experience: of 1931 admissions, 31% were due to AR! (pneumonia and severe pneumonia) with a CFR of 9% (Z. Rasmussen, personal communication). Unpublished Pakistan data from the Children Hospital, Pakistan Institute of Medical Sciences (PIMS), islamabad. in the 12 months from November 1988, children under five with AR! accounted for 26% of outpatient department (OPD) visits, 25% of admissions and 38% of all inpatient mortality. Of the AR! deaths, 65% were due to pneumonia alone, 17% pneumonia and diarrhoea, 4% pneumonia and measles. Compared to the number of inpatients dying of diarrhoea, ARI was twice as common in neonates, equally as common in post-neonatal infants and one third as common in 1 to 5 year olds. The urban PHC sites of the Department of Community Health Sciences of the Aga Khan University serve about 50,000. Population-based mortality data (unpublished) show an ARI-specific proportionate mortality ratio of 9-11% between 1989-1991. These figures are conservative because no case with a primary cause of death as breathing problem was included in the analysis given the lack of specificity. Moreover, diagnosing fatal ARI by verbal autopsy (or even non-fatal AR! by maternal interview) is imperfect. The findings are, then, consistent with international experience which would predict a mortality ratio of approximately 15% in the absence of pertussis and measles deaths as in the urban PHC programme. Ghafoor et al²⁵ conducted an important investigation into the causative pathogens of AR! in the BOSTID series. They studied 1492 cases of in and outpatients over two winters, 1986-1988, in Rawalpindi and Islamabad. They isolated a viral pathogen in 37% of cases of which 89% were RSY (of these 26% had simultaneous positive blood culture). H. influenzae and S. pneumoniae were each isolated in 10% of cases. One third of the former were non-typable H. influenzae. Particularly noteworthy was the clinical difficulty in...
distinguishing bacterial and viral AR; that is, wheezing did not make serious bacterial disease less likely. Of interest is that of mother who denied treating their ill children, 21% of these children had positive urine tests for antibiotics. Mothers did not know or were not willing to disclose that medicines were being taken. The same group extended their findings in reporting the antibiotic sensitivity patterns. Only 71% of H. influenzae were sensitive to co-trimoxazole in vitro. Only 81% of pneumococci were sensitive to penicillin. The potential implications for case management are obvious. Finally, striking seasonal variation was confirmed, peaking in the mid-winter months of December and January. Risk factors abound in both rural and urban settings. In rural areas there are both epidemiologic and health system risks. That is, household unawareness, inaccessible allopathic health care, ineffective case management by traditional healers, allopathic providers unfamiliar with modern treatment recommendations and inconsistent drug supplies are common. Add to this, wide-spread childhood malnutrition, low birth weight, crowded living quarters (8-12 in a single room for both cooking and sleeping), incompletely immunized children, dusty environment, biomass fuel for cooking and warmth, and general poor hygiene. On the other hand, breast feeding is widespread and extreme winter cold is not universal. The urban situation is similar except that the health services are somewhat more favourable.

**Community intervention studies in Pakistan**

Pakistan has contributed an important community intervention trial. Khan et al. reported their experience in Hazara between 1985-1987. Key design features included: (1) 31 intervention villages and 7 comparison villages which received the intervention during year 3; (2) CHWs with at least 10 years of schooling who visited each household every 10-14 days for active case finding; (3) extensive maternal health education regarding ART recognition and evaluation as well as other PHC messages; (4) annual maternal ART knowledge, attitudes and practices (KAP) surveys; (5) usage of a protocol similar to present WHO recommendations. The main findings were an AM-specific mortality rate of 6.3/1000 per year in the intervention villages compared to 14.4 in the comparison villages. One year after introducing the ART control measures to the latter, their rate dropped to 6.5/1000 (p = .06). Total child mortality was 29/1000 vs 39/1000 in the intervention and control groups, respectively. Other findings included a 16-25% higher (not statistically significant) ART mortality rate in female vs male children. KAP surveys confirmed that maternal practices had changed during the study. Initially 60% of mothers sought traditional or religious healers for childhood cough and fever vs 16% who sought allopathic treatment. The percentages were reversed by the end of the study. A brief, informal report of a second study was made by Khan et al. (unpublished data). Two physicians visited two villages every other day during February-April 1991. They studied children under five who presented to the PHC centre. Seventy-six percent of encounters were diagnosed as URI, 15% pneumonia and 0.3% severe pneumonia. Patients diagnosed with pneumonia were treated with co-trimoxazole and only 6% needed a change to amoxicillin on follow-up. Of those presenting clinically with presumed viral URI (“cough and cold”), only 1% required antibiotics on follow-up.

So, in this facility-based “community” study, 20% of ART was clinically diagnosed as pneumonia. Of note, 69% of the presenting patients were male so the findings may not represent the true community experience. Furthermore, co-trimoxazole was far better in vivo than in vitro as reported by Ghafoor et al. The possibility of diagnostic misclassification exists, yet the setting anticipates the national control strategy wherein practitioners must make decisions on incomplete information.

**Other Pakistani studies**

The only available nation-wide information relates to health systems research. This monthly monitoring system from the PHC Project (Limprecht, N. - unpublished data) receives reports from 160 centres throughout Pakistan and summarizes provider diagnoses and treatments. Tentative inferences about disease patterns, physician practices and drug supply logistics can be made. Despite validity questions due to incomplete and possibly inaccurate reporting, one observes the pattern that providers
tend to over-prescribe antibiotics, but ironically the drugs are often not available in government health facilities. Khan has just completed an anthropological study of 315 mothers in 4 villages in the Islamabad area enquiring about knowledge, attitudes and practices regarding both URI and pneumonia in children. Some of their important findings included: 100% recognized the term “pneumonia” (93% for dard); 48% of mothers had experience with pneumonia in one of their children; diagnostic clues included “difficult” breathing (91%), but not “rapid” breathing (13%) nor chest indrawing (2%); the most common home remedy was chest-binding (36%); virtually all (94%) would seek an allopathic doctor. The study defined perceptions of primary caretakers, the mothers. Many were accurate and should be encouraged and enlarged upon; some practices, however, were unhealthful and should be sensitively discouraged. Findings from a 1991 unpublished survey in a kachchi abadi affiliated with the Aga Khan University provided insight into the knowledge and practice of low-income urban mothers. Questionnaires were administered to 285 mothers of children age five. Perceptions regarding their community’s most common childhood diseases and causes of childhood death were accurate as was known regarding risk factors for acquiring ARI (71% recognized at least 10 of 13 factors). On the other hand, 57% of respondents reported at least 4 of 8 risk practices. Actual behaviour might have been more high risk. These practices correlated with household income but not with maternal literacy or maternal knowledge. In October of 1990, D’Souza (unpublished data) performed a cross-sectional study in Essa Nagri, another AKU PHC site. She surveyed 350 structures which housed 35% of the under five year old population. Through questionnaire and physical measurements, she assessed childhood illness in the preceding two weeks and various physical, environmental and social risks. Of the 36% of children with recent illness, 32% had respiratory symptoms (vs 24% with diarrhoea). Risk factors associated with ART included: families with more than one child under five, poor ventilation (as measured by humidity differentials), crowding, small plot size and poor housing construction.

The national ARI control programme

The National ART Control Programme was launched in 1989 supported by WHO, UNICEF and USAID. Its main objectives are:
1. To reduce the severity of and mortality from pneumonia in children,
2. To reduce the incidence of ALRI
3. To reduce the severity of and complications from, AURI
4. To rationalize the use of antimicrobial and other drugs for the treatment of ARI in children.

The First National ART Workshop, in December 1989, recommended: focusing on case management; establishing an information system; conducting a national baseline survey and providing provincial workshops for ARI programme managers and case management workshops for physicians. The Second National ARI Workshop, in January 1990, recommended: adopting the WHO case management chart with co-trimoxazole as the first-line drug; reviewing existing URI medications; designating salbutamol as the first-line drug for wheeze and making it generally available and emphasizing breast feeding, growth monitoring, antenatal care and avoidance of exposure to tobacco and fuel smoke as health promotive and disease preventive measures. Research initiatives will study the antimicrobial sensitivity patterns of the principle pathogens and mothers’ knowledge and actions regarding childhood ART.

DISCUSSION

World-wide experience shows that community ART control programmes are effective and efficient interventions to reduce child mortality. Unfortunately, to date no urban intervention programmes have been reported. This may represent the desire of investigators to minimize the complicating effects of multiple health services or source of health information. However, valuable lessons can be learned. First is the usefulness of the WHO algorithm. Second, the effectiveness of the visual impression of tachypnea in situations of inability to count or lack of watches is encouraging. Third is the impressive
performance of TBAs and CHWs, albeit in closely supervised situations, in diagnosing and treating life-threatening illness. Fourth is the usefulness of health education in modifying household ART management. Fifth is the limitation of active case-finding especially for young infants who can fall ill and die within 4 days of onset of illness. Sixth is the consistent and sustained reduction in both ART and non-ART mortality rather than replacement mortality”. One conclusion is that the decreased morbidity from a recognized and promptly treated ART leaves the child less fragile to combat the next infection. The Pakistan community study is consistent with all of the above. Of note, policies for prescribing and dispensing antibiotics by non-physicians are evolving. The Pakistan Nursing Council allows lady health visitors to prescribe within the community setting with the implication of proper training and supervision. The relatively new role of community health nurse requires that her practice be defined by her sponsoring institution. Health planners include community health workers as key health care providers for the future. Their role (and by extension that of TBAs) in drug treatment raises complex, unanswered questions. Pakistan also has the unusual laboratory findings of 36% TI. influenzae isolates being non-typable and a high in vitro resistance of these to co-trimoxazole despite preliminary in vivo efficacy. These findings are actively being studied further in two of the three ongoing national ART investigations. Pakistan has poor social indicators: health, education, female status and so on. Gender discrimination can be inferred from facility-based data unless girls are truly more resistant to ART which is unlikely. All of the known risk factors for ART are wide-spread. Asthma and pneumonia are frequent in children and diagnostic confusion between the two is well known29. Both present similarly and each is a risk factor for the other. Northern areas and urban AKU morbidity patterns consistently show that asthma is as common as pneumonia. In USA, asthma is beginning to receive the attention of public health practitioners as the most common chronic disease of childhood30. Certainly it will be on Pakistan’s health agenda as it proceeds through the health transition. In the meantime, teaching a standard approach to the wheezing child and rationalizing the use of drugs for the treatment of tachypneic children as outlined in the National ART Control Programme is a logical starting point. Reducing diarrhoeal disease mortality has been possible through oral rehydration and risk reduction measures. Decreasing mortality due to ART is more difficult, however. One explanation is that the family must interact with the health system. The National ART Control Programme is ambitious and complex. The multiple algorithms by age, syndrome and severity are challenging. Also only 16% of the populace is served by the governmental health system31, the first audience targeted to receive training in ART. Uncertainty regarding “first-line” drug efficacy (especially in urban areas where drug resistance due to more extensive misuse is likely to be greater) is of concern. Additionally, too few household “knowledge, attitudes and practices” studies have been performed. And, since control measures are in their infancy, no known ART health systems research studies have been reported. Meanwhile, as you read this paper, several Pakistani children will have died due to ART, one every 2 minutes. Despite incomplete information and an imperfect plan, three actions are recommended, each familiar to the medical profession: proceed with available information, encourage further research and ensure rapid dissemination of the findings. Therefore, the National ART Control Programme must be implemented with all possible speed. Mistakes will be made which must be acknowledged, analyzed and shared. Pneumonia has emerged as a leading cause of death among children under five. Inexpensive medications can save most of them. We must make the treatment accessible to all and make tomorrow a reality for the many innocent ones condemned to die.

REFERENCES

2. Allen, SR. Acute respiratory infections, in ARI - National Programme for the control of acute