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Respiratory Viruses- New data and Perspective from Pakistan

Respiratory viruses like Influenza, respiratory syncytial virus (RSV) and human metapneumovirus (HMPV) are increasingly being recognized as important causes of both upper and lower respiratory tract infections in developing countries. Even the bacterial pneumonias are often preceded by viral infections, which 'plough the field' for these secondary bacterial infections to occur. Viruses have traditionally gotten little attention because of the somewhat understandable attitude of the medical community, which asked, 'why should we care about these viruses if we cannot do anything about their prevention or treatment?' Antivirals are of no use for most patients and no clear preventive strategies were available until recently. However, things are rapidly changing in these domains and new data are emerging.

The question of what are the common respiratory viruses in Pakistan has started to be answered by some recent studies. A study in Abbassi Shaheed Hospital, Karachi found that 36% of the severe pneumonia cases in hospitalized children < 5 years old were associated with RSV, HMPV or Influenza virus.[1] This is consistent with other regional studies which report isolation of viruses in 30 to 50% of hospitalized pediatric pneumonia cases in developing countries. RSV was most common during the rainy season of July to September in Karachi, which may be one of the factors behind the community belief that playing in the rain gives the child a cold. HMPV was more common during the winter season, and this may explain at least part of why cough and cold illnesses are increased during winters. While the data on seasonality of respiratory viruses is so far limited in Pakistan, more studies are in process which will be better able to explain the burden and seasonality of these respiratory viruses in both urban and rural settings, as well as diverse geographical locations within the country.

Influenza is perhaps the most important respiratory virus of all, mainly because of its ability to cause pandemics and because it often causes more severe illness than other respiratory viruses. The influenza A(H1N1) pdm09 virus caused a global pandemic from June 2009 to August 2010. However, little data was so far available on the influenza A(H1N1) pdm09 burden within Pakistan. A recent study at the Aga Khan university is the first to show that influenza A(H1N1) pdm09 did affect the children in Karachi during and after the pandemic period, and these infections were associated with increased morbidity and mortality.[2] Overall, Pakistan was fortunate that A(H1N1) pdm09 did not affect the country as bad as some other countries, but lessons should be learnt from this experience and better arrangements need to be made for coping with future influenza pandemics.

Influenza is the only respiratory virus whose vaccine is commercially available in the world. In Pakistan, the influenza vaccine became first available in November 2006, but its use has been quite low even during the pandemic period. One reason for the lack of excitement in the medical community regarding the use of influenza vaccine is the lack of data regarding its efficacy within Pakistan. The emerging data on influenza burden within Pakistan may help in this regard. It should be noted that WHO recommends influenza vaccine for all pregnant women across the world in view of its benefits to both mother and child. Influenza vaccine can be given to all healthy individuals above the age of 6 months.

Antivirals against influenza are also available and can be lifesaving in the correct situation. In order to get the most out of these antivirals, seasonality of influenza needs to be known, and low cost diagnostic tests need to be made available to quickly identify the patient with influenza. A lot of work is being done to identify easy to use, low cost diagnostic tests for influenza at the bed side and this technology should be widely available in the Pakistani hospitals in the coming few years.

The current preventive strategies for RSV, which include the monoclonal antibodies administered to high risk babies, are very expensive and not very feasible in the developing country settings. The available repertoire of antivirals against RSV and HMPV are also not effective or feasible. However, research is being conducted to find effective vaccines for these viruses. Once these vaccines are discovered, they are likely to be quickly taken up in the developing as well as developed world, given the significant burden of these viruses.

Until the time when effective vaccines and antivirals are available and even afterwards, the basic infection prevention strategies of hand hygiene and standard precautions remain the key for prevention of respiratory viruses. Current evidence supports the use of influenza vaccine in Pakistan, in particular in the high risk groups and in pregnant women. Major advancements in the diagnosis, prevention and treatment of respiratory viruses are expected in the coming few years.

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ORIGINAL ARTICLE

A Review of Antimicrobial Resistance for Common Pediatric Infections in Pakistan -Time for Pediatricians to Do More!

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Abstract

Background
Antimicrobial resistance to old and new antibiotics has alarmingly increased worldwide including Pakistan. This trend has been documented in health care facilities, particularly in high-risk areas such as intensive care units, surgical units and neonatal intensive care units, over the last few decades. Children of all ages, including neonates, have been equally affected. The treatment of several pathogens, including *methicillin-resistant Staphylococcus aureus* (MRSA), *penicillin-resistant Streptococcus pneumoniae* and *vancomycin-resistant enterococci* (VRE), resistant tuberculosis, malaria is problematic. In this article we review the available pediatric data available on antibiotic resistance in Pakistan.

Materials and Methods
Articles from both international and local literature were selected using search words "pediatric infections", "antibiotic resistance", "culture and susceptibility" and "children" in PUBMED and PakMedinet. All articles up till 2008 were included.

Results
In Pakistan nearly all neonatal and childhood infections have consistently shown a rise in resistance to both traditional and alternative antimicrobials. Pathogens causing neonatal infections have resistance rates of more than 50%. Diarrheal pathogens such as *shigella* and *cholera* are resistant to first line agents and even second line agents. Typhoid has considerable resistance to first line drugs with rising resistance to quinolones and third generation cephalosporins. The common respiratory pathogens *Haemophilus* (*H) influenzae*), *Moraxella* (*M) catarrhalis* and *Streptococcus (Strep) pneumoniae* in few studies have documented resistance in 10-70%. MRSA is up to 30% of *Staphylococcus* isolates. Malaria resistance is up to 35%. In tuberculosis (TB) resistance (~50%) and MDR TB (>2%) has also emerged as a major threat in the control of TB. Data for other common infections such as urinary tract infections and skin and soft tissue infections have also shown similar trends. The presence of these resistant organisms translates into a high morbidity and mortality besides significant economic burden. Various factors have contributed to this including indiscriminate misuse of antibiotics, nonexistent infection control policies, nonexistent microbiologic facilities and research.

The inappropriate use of antibiotics remains a common and well-recognized practice. It is estimated that at least 20-50% of antibiotics are unnecessarily prescribed.

Conclusion
The inappropriate use of antibiotics remains a common and well-recognized practice. The presence of these resistant organisms translates into a high morbidity and mortality besides significant economic burden One practical solution is the judicious use of antibiotics by all clinicians. All stakeholders should be mobilized including physicians, infectious disease specialists, nurses, hospital administration and government for this noble purpose.

Key words
Antibiotic resistance, antibiotic misuse, pediatric infections, children

Introduction

Increasing antibiotic resistance has been alarming and has emerged as a major health threat in not only in west but also in resource poor countries of Asia.[1-3] This increasing trend has been documented in all health care settings, particularly in high-risk areas such as intensive care units, surgical units and neonatal intensive care units, over the last two decades. Realizing the global threat of drug resistance WHO in 2001 developed *"The WHO Global Strategy for Containment of Antimicrobial Resistance"* that provided some key interventions to slow the emergence and reduce the spread of antimicrobial-resistant microorganisms.[1]

The emerging antibiotic resistance has also affected children in all ages, including neonates.[4]

The empiric use of "conventional" antibiotics for common pediatric infections is likely to fail with poor outcomes if the etiologic agents are resistant. Mortality and morbidity attributable to drug-resistant microorganisms have increased manifold. Complications, longer hospital stay; invasive diagnostic and therapeutic interventions including the use of newer antibiotics all add to the cost.[5] The burden of this cost is large for a resource limited country like Pakistan. Over last two decades there has

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been a gradual accumulation of mostly crude data about antibiotic resistance in Pakistani children with a host of infections and antibiotic resistance pattern to suggest the enormity of the problem.[6-8] We acknowledge that these and similar studies have mostly been not well designed, without proper microbiologic standards and leave more questions than answers elucidated later. However we will review below the available pediatric data available on antibiotic resistance in Pakistan and discuss management implications of common infections based on these "evidences."

Material and Methods

Articles from both international and local literature were selected using search words "pediatric infections", "antibiotic resistance", "culture and susceptibility" and "children" in PUBMED and PakMedinet. Those articles were selected that included Pakistani children till March 2008. Some articles that had adults and children were also included. Also some recent articles (2010-2012) were also reviewed if relevant.

Neonatal Infections

World Health Organization (WHO) estimates that more than two-third of all infant mortality worldwide occurs in the neonatal period.[6] More than 33% of these deaths is due to neonatal infections (sepsis, pneumonia and meningitis). In Pakistan more than 25-50% of all neonatal deaths are attributable to infections.[7-9] This in itself is a huge burden of a preventable illness. In addition to this the problem of drug-resistant organisms has been increasingly recognized in most neonatal intensive care units (NICUs). In Pakistan this not only adds to difficulty in management, increased costs but also mortality.[7-9] The major reasons have been unhygienic labor practices, poor infection control practices and indiscriminate & inappropriate use of antibiotics. This translates in a vicious cycle of more use of expensive and scarce antibiotics, creating newer resistant mutant microorganisms.

Bhutta *et al* described two third of culture confirmed neonatal sepsis cases among gram-negative organisms as resistant to first line therapy, i.e., ampicillin and gentamicin (Table 1).[10] However another larger study of 512 neonates from Naval Hospital Karachi showed much higher resistance rates.[11] A study of 233 neonatal cultures by Maqbool *et al* showed *S. aureus* and *E. Coli* as common infectious agents.[12] Resistance to cefotaxime, ceftazidime and amikacin was 34% to 80% and to ciprofloxacin 13% to 72%. This resistance to first line drugs led to a four times higher mortality in early onset sepsis cases. A study of 109 culture-proven neonatal sepsis showed both gram-positive *(enterococcus* and *S. aureus*) and gram-negative organisms (*Klebsiella spp.*) as major pathogens with very resistance to all first line antibiotics (see Table 1).[13] More than 60% of *S. aureus* isolates were MRSA and that more than 90% gram-negative rods (*K. pneumoniae, E. coli* and *acinetobacter baumannii*) were resistant to ampicillin, gentamicin and cotrimoxazole. Also resistance was 25-75% to the third generation cephalosporins and ciprofloxacin.

A large study conducted by Rahman *et al* at Khyber Teaching Hospital, Peshawar[14] shared a total of 1003 out of 1598 blood cultures were positive. *E. coli* was the most common organism found (36.6%), followed by *S. aureus* (29.5%), *Pseudomonas* (22.4%), *Klebsiella* (7.6%), and *Proteus* (3.8%). They found that *E. coli* and *Pseudomonas* (23-93%) showed a high degree of resistance to commonly used antibiotics (ampicillin, augmentin, and gentamicin), a moderate degree of resistance to cephalosporin (cefotaxime, ceftzidime, and ceftriaxone), and low resistance to drugs not used for newborn babies (ofloxacin, ciprofloxacin, and enoxabid). *S aureus* showed a resistance to all three groups of antibiotics (26-73%). However there have been apprehensions with the methodology and reported culture results.[15]

A year long data in the following year in another study at the same institution included 67 neonates with positive cultures.[16] *E. coli* (80%) was the commonest organism causing both early and late onset sepsis,. Along with other gram-negative organisms it showed high degree of resistance to commonly used antibiotics and comparatively low resistance to gentamicin, tobramycin, imipenem, amikacin, fluoroquinolones respectively (Table 1). Though numbers were small the results were much different in terms of etiologic agents and susceptibility.

Another smaller study from Dow Medical College, Karachi in 64 positive culture cases (*E. coli* 54%, *K. pneumoniae* 21%, *Enterobacter aerogenes* 16%) showed maximum sensitivity to ceftazidime, amino glycosides and ceftriaxone.[17] A much larger study of 319 positive neonatal blood cultures from National Institute of Child Health, Karachi revealed gram negative organisms (92%) being common with high resistance with ampicillin (83-100%), cefotaxime (83-100%), ceftazidime (73-100%), imipenem (0-81%) and ceftriaxone (66-100%) being main antibiotics.[18] Batool *et al* compared two time periods (1984-85 vs 2001-2002) for sensitivity pattern in neonates.[19] During the later period 100 positive blood cultures (*Klebsiella* 24%, *S. aureus* 22%, *Pseudomonas* 20%, *Enterobacter* 9% and *E. coli* 9%) were evaluated. The mean sensitivity to ampicillin was 13%, tobramycin 34%, gentamicin 39% and cefotaxime 35%. Although the spectrum of organisms was similar to that studied twenty years prior in the same environment, the sensitivity pattern had dramatically changed to resistance in two-third to more than three-fourth to common antibiotics (Table 1).

A more recent study from Multan showed a high degree of resistance to commonly used first line antibiotics in neonatal sepsis.[20] Among 62 culture proven sepsis cases (*E. coli* 37%, *Klebsiella* 10%, *S. aureus* 32%) resistance to ampicillin was 100%. *E. coli* showed resistance to ceftriaxone or cefotaxime 25%, ceftazidime 32%, imipenem 20%, and ciprofloxacin 48%. A larger study by Tayyaba *et al* highlighted the importance of

the need to modify existing antibiotic protocol in NICU.[21] They looked at 524 positive cultures. Commonest organisms included *E. coli* (32%), *S. Epidermidis* (25%), *Klebsiella* (19%) and *Pseudomonas* (15%). Amikacin was the most effective drug followed by co-amoxicillin clavulanic acid, ciprofloxacin, imipenem and ceftazidime in that order. Resistance against ampicillin and gentamicin was again very high.

Although these studies have been done in different setups (for example large and small teaching hospitals, community based and tertiary care hospitals) with lack of or incompletely mentioned microbiologic isolation methods, they have shown similar trend over last decade in terms of high and increasing resistant organisms in the neonatal period (Table 1). Less common organisms are replacing the traditional neonatal pathogens not only as the hospital- but also as community-acquired infections.[22] The morbidity and mortality results have been depressing. The great dilemma has been that empiric antimicrobial therapy (ampicillin and gentamicin) for neonatal sepsis is now being questioned in most clinical scenarios. Coming up with an alternative antibiotic regimen would be equally challenging. Individualized and institutional based decisions would be more appropriate. Additionally strict infection control policies, limiting inappropriate antibiotic use (routine overuse of cephalosporins or carbapenems) and periodic review in each NICU would address some of these challenging issues.

Diarrheal Diseases

Diarrhea related deaths in children are estimated to be 2 million, most of whom are under 5 years of age.[23] This preventable disease has astonishingly increased risk of mortality in children with severe malnutrition and sepsis which are also common in our setup.[23-30] These studies have often highlighted the need to improvise methods to decrease morbidity and mortality in young children.

Stool cultures are often not done routinely in Pakistan. However pathogenic enteric isolates are often implicated in acute gastroenteritis (GE). One study from Aga Khan University Hospital among 6670 stool samples from children and adults showed distinct seasonal variation with most cases in summer.[25] It also showed that common isolates included *Vibrio cholera 01 Ogawa* (33%), *Campylobacter jejuni* (17%), *Enteropathogenic E. coli* (10%), *Salmonella paratyphi b* (7%) and *Shigella flexneri* (6%). Similarly the burden of shigellosis is high in resource-poor countries. A prospective, population-based study in six Asian countries (including Pakistan) was done in >600,000 persons of all ages showed *Shigella* species in 2,927 (5%) of 56,958 diarrhea episodes.[26] *Shigella flexneri* was the most frequently isolated. The majority of *Shigella flexneri* isolates in each site was resistant to amoxicillin and cotrimoxazole. Ciprofloxacin-resistant *Shigella flexneri* isolates were also identified. Thus it appears *Shigella* antibiotic-resistant strains of different species and serotypes have emerged. Khalil *et al* reported from 152 stool cultures from as many children with bloody diarrhea.[27] Cultures were positive in 19% for *Shigella spp.*, 8% for *Campylobacter* and 5% for *Salmonella.* Among *Shigella species, Shigella flexneri* (8%) was the most frequently isolated species, followed by *Shigella dysenteriae* (7%), *Shigella boydii*, (3%) and *Shigella sonnei* (1%). All *Shigella* isolates were susceptible to nalidixic acid (100%) but susceptibility was very low to cotrimoxazole (7%) and ampicillin (4%). A cross-sectional study from slum areas in Karachi in children with gastroenteritis showed isolation rate of 4% (193/4688 stool samples) for *Shigella species* (*Shigella flexneri* 58%, *Shigella sonnei* 16%, *Shigella boydii* 15% and *Shigella dysenteriae* 11%).[28] All isolates were susceptible to ofloxacin and ceftriaxone (Table 1). However resistance was high to commonly used antibiotics (cotrimoxazole 88%, ampicillin 56% and nalidixic acid 39%). This contrasts to the study by Khalil *et al* in which isolates were susceptible to nalidixic acid[27] and another study from in Karachi in 2002-4 in which resistance to cotrimoxazole was 56-89%, ampicillin 4-87% but nalidixic acid was 0%.[29] Thus treatment options are becoming limited in cases of severe dysentery due to *Shigella*.

Vibrio cholerae (V. cholerae) has remained one of the major etiologic agent responsible for hospitalization, morbidity and mortality in children with diarrhea.[30] In Pakistan cholera outbreaks until recently have highlighted it's continued presence and threat.[31-42] A 7 year data from AKU, Karachi (1990-6) looked at the microbiologic, temporal, and demographic trends in *V. cholerae* infections (Table 1).[36] Eight hundred and eighty eight (888) strains of *V. cholerae* (*V. cholerae* serogroup O1, 64% and serogroup O139, 36%) were isolated in specimens from 886 patients including children. Of these 44% of all isolates were in children less than 5 years of age and 27% were in less than 2 years of age. There was no resistance to ofloxacin, variable to erythromycin and chloramphenicol but was nearly 100% to naladixic acid, cotrimoxazole and tetracycline (Table 1). Although emergence of resistant strains was observed, serogroup O139 had disappeared by 1996.

Nizami *et al* looked at 4346 children hospitalized with gastroenteritis during 1990-5.[37] Of these 348 children (8%) were confirmed to have cholera. The mean age was 31 +/- 34 months. Most cases were due to *V. cholerae Ogawa biotype Eltor* but the new strain, i.e., *V. cholerae 0139* was isolated in 14% cases in 1994. The sensitivity of *V. cholerae* has also changed (Table 1). In 1994, the organisms were resistant to commonly recommended antibiotics (Tetracycline 0-83%, co-trimoxazole 100% but none to third generation cephalosporins, ofloxacin, nalidixic acid, ampicillin and erythromycin). The sensitivity of 212 isolates of *V. cholerae* EIT or serotype Ogawa was done at Children's Hospital, Pakistan Institute of Medical Sciences (PIMS), Islamabad.[38] Variable resistance of the organism to the commonly used anti-cholera drugs was seen with 100% sensitivity in 1998 but falling to 39% in 1999 (Table 1). Another study from Karachi during the same period

of 846 stool specimens from children showed 161 (19%) were positive for *V. Cholera*.[39] Resistance was high to some (nalidixic acid 100%, chloramphenicol 14-18%, doxycycline 25-33%, cotrimaxazole 100%) but none to cephalosporins and quinolones (0%). A more recent study from Children's Hospital, PIMS in children < 12 years age with acute gastroenteritis showed that all cases were of *V. Cholera Eltor biotype Ogawa*.[41] All were resistant to nalidixic acid but sensitive to doxycycline, ofloxacin, ciprofloxacin and erythromycin.

Jabeen *et al* reported the re-emergence of *V. cholerae* O139 in Karachi in 2000-2001.[42] A total of 144 stool cultures were found to be positive for *V. cholerae* O139 in comparison with 545 *V. cholerae* O1 especially from older population. Changing sensitivity pattern of 2000-2001 *V. cholerae* isolates was observed compared to that of 1993-1994. In the first period isolates were resistant to cotrimaxazole (99%) and chloramphenicol (35%) whereas the recent isolates are almost 100% sensitive. These studies have shown that different strains of *V. cholera* will continue to have seasonal and temporal periodicity and potential for large outbreaks.

These diarrheal diseases patterns, specifically for cholera tell us about the difficulties in current therapy of such a common infection in children. For cholera given the resistant data, ciprofloxacin or azithromycin as single dose would be first choice of therapy. Within the global perspective there is a strong and committed need for ensuring adequate public health measures to prevent the occurrence of outbreaks such as *shigella* and *cholera*. Educating the public about the dangers of drinking contaminated water would go a long way in this regard.

Typhoid

Globally, the new estimated yearly typhoid burden is more than 21 million cases with more than 0.2 million deaths and that due to paratyphoid fever more than 5 million.[43] A conservative estimated incidence ranges from 150 per 100,000 population in South America to over 1000 cases per 100,000 population in some Asian countries. In children it is a very common infection especially those who are <5 year old.[44] Mortality may reach up to 10%. These figures are further complicated by the emergence of drug-resistant strains of *Salmonella typhi (S. typhi*) to both first-line and even second-line antibiotics such as quinolones and third generation cephalosporins even in Pakistan as shown below. Drug-resistant strains that are resistant to ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole are called multi-drug resistant or MDR strains of *Salmonella.*

There is ample resistance data from Pakistan to suggest that typhoid has become a major problem. A 4-year data from Aga Khan University from late 1980's in 355 children with culture proven typhoid showed an overall resistance of 20% to first line drugs (ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole, Table 1).[45] These children infected by MDR strains of *salmonella* were sicker, "toxic" and had higher mortality. Hundred children with typhoid from Peshawar showed an in-vitro resistance figures for amoxicillin, chloramphenicol and cotrimaxazole as 82%, 83% and 95% respectively.[46] MDR was found in 18% isolates. However the isolates showed a good sensitivity to ofloxacin (100%), ciprofloxacin (98%), cefotaxime (88%) and ceftriaxone (86%) respectively. Varying rates of resistance have been reported from smaller studies in Karachi and Peshawar.[47,48] While all isolates were sensitive to ciprofloxacin and ofloxacin, sensitivity to third generation cephalosporin's was 57-79%. Such high resistance is worrying but data must be interpreted with caution as no MICs were done.

A large study of 2551 isolates of adults and children (*S. typhi* 80%, *S. paratyphi* A 20%) showed increasing MDR trend to conventional first line drugs (chloramphenicol, ampicillin, cotrimaxazole) over a six year period.[49] *S. typhi* resistance was <10% in 1989 but it increased to 66% in 1990, 56% in 1991, 49% in 1992, 57% in 1993, 67% in 1994 and a high figure of 75% in 1995. However, no *S. typhi* was found resistant to fluoroquinolones or third generation cephalosporins (ceftriaxone and ceftizoxime). *S. paratyphi A* isolates were however found susceptible to both the conventional and second line drugs. Mobeen *et al* also reported a high resistance of 72% of *salmonella* blood isolates in children.[50] Bhutta in a large series of 876 children with culture-proven typhoid reported a high proportion of cases infected with MDR strains (32%).[51] Using a third-generation cephalosporin the outcome (<1% fatality) improved significantly but time to defervesce was significantly longer among MDR strains and involved a high cost of treatment.

Saqib *et al* too had shown high resistance to first line of drugs for the treatment of typhoid (Table 1).[52] Similarly, high rates of resistance to first line antibiotics was shown from Rawalpindi.[53] Bilquis *et al* from National Institute of Child Health, Karachi reported 100 children (5-10 years) with positive cultures (95% positive for *S. typhi*) with all susceptible to all first line drugs and cephalosporins.[54] However Tabish *et al* found a cumulative prevalence of 67% of MDR *S. typhi* in children in Islamabad.[55] The cumulative cure rate with conventional therapy (chloramphenicol or amoxicillin) was 47.4%. MDR isolates were associated with higher failure rate, longer hospitalization and a delay to defervesce.

At the Armed Forces Institute of Pathology, Rawalpindi an apparent changing and mixed trend in salmonellae species causing typhoid and also the drug resistance pattern was seen.[56] Over a seven year period there were *S. typhi* (54%) and *S. paratyphi A* (46%) blood isolates from adults and children. There was higher isolation rate for S. paratyphi A. The resistance to conventional drugs in *S. typhi* decreased dramatically from 80% to 14%, while in *S. paratyphi A* resistance from 14 to 44% (Table 1). More concern seems to be the apparent decreased susceptibility to the fluoroquinolones but there was no resistance to third generation cephalosporins during both periods. A similar

study by Ali *et al* looked at 333 blood isolates of *S. typhi* and *S. paratyphi A.*[57] MDR was found in 172 (52%) isolates. None of the isolate was resistant to ciprofloxacin, ofloxacin and ceftriaxone.

These studies reveal that resistant typhoid is rampant. *S. paratyphi* and MDR strains may be becoming more prevalent and also proving difficult to treat with conventional drugs adding to costs and morbidity. Despite this there is consensus that the traditional first line drugs should still be used as empiric therapy in uncomplicated enteric fever pending culture results. First line therapy in children due to possible MDR isolates should be oral cefixime or IV ceftriaxone (for toxic children). Alternative agents for fully susceptible *S. enterica* serotype *typhi* strains include ampicillin, trimethoprim-sulfamethoxazole, high dose ciprofloxacin or ofloxacin, chloramphenicol and azithromycin.

Pneumonias

According to WHO 20% of all deaths in children under 5 years are due to acute lower respiratory infections (pneumonia, bronchiolitis and bronchitis); 90% of these deaths are due to pneumonia mostly in third world countries.[58] Pneumonia kills more children than any other illness – more than AIDS, malaria and measles combined. Over 2 million children die from pneumonia each year, accounting for almost 1 in 5 under five deaths worldwide. The bacteriological confirmation of childhood pneumonias is difficult and etiological data is scant.

The National Acute Respiratory Infection (ARI) Control Program case management guidelines have resulted in a significant reduction in the case fatalities, antibiotic use and cost of management.[59,60] The Pakistan Co-trimoxazole Study Group did a randomized controlled trial of 595 children, aged 2-59 months, with non-severe or severe pneumonia (WHO criteria) and were randomly assigned on a 2:1 basis co-trimoxazole (n=398) or amoxicillin (n=197) groups.[61] There were 23% therapy failures in the co-trimoxazole group and 15% in the amoxicillin group (p=0.03). Also there was no significant association between antimicrobial MIC and outcome among bacteremic children treated with co-trimoxazole. They thus concluded that co-trimoxazole provided effective therapy in non-severe pneumonia and amoxicillin to be more effective for severe pneumonia.

This clinical effectiveness of co-trimoxazole does not correlate well with the in vitro studies with a high resistance of 78%-80% to co-trimoxazole among *Strep. Pneumoniae* isolates and 59%-61% among *Haemophilus influenzae* (*H. influenzae*) isolates.[62] Despite this another randomized controlled clinical trial by the Catch-up Study Group showed that both amoxicillin and co-trimoxazole were equally effective in non-severe pneumonia.[63] Treatment failure in the amoxicillin group was 16% compared to 19% in the co-trimoxazole group. Also a recent study by the Pakistan COMET (Cotrimoxazole Multicentre Efficacy) Study Group in a randomized controlled multicentre trial in seven hospital outpatient departments and two community health programmes showed almost same results.[64] A total of 1134 children (2-59 months olds) with non-severe pneumonia were randomly allocated to receive standard or double dose of co-trimoxazole orally twice-daily for 5 days. Treatment failure occurred in 19.4% in the standard group and 21% in the double-dose group (relative risk 1.10; 95% CI 0.87-1.37). A subsequent nested study by Tabish *et al* followed the clinical course of non-severe pneumonia in children aged 2-59 months using alternative therapy failure criteria. Using alternative therapy failure criteria only 3.5% children were labeled as therapy failure compared to 10.8% using current WHO criteria.[65] A more recent study using the same methodology by using standard versus double dose of oral amoxicillin was done by Tabish and his colleagues to overcome the MIC of *Strep. Pneumoniae* and *H. influenzae* for amoxicillin.[66] This double blind randomized controlled trial involved 876 children, aged 2-59 months, with non-severe pneumonia and were allocated to receive either standard (45 mg/kg/day) or double dose (90 mg/kg/day) oral amoxicillin for 3 days and then followed up for 14 days. The cumulative therapy failures were 6% with standard and 8% with double dose amoxicillin (Not statistically significant).

Despite limitations of these large and robust studies, such as lack of an etiologic diagnosis and fairly high failure rates, the WHO recommends the IMCI strategy for the ARI programs. The diagnosis is based on clinical criteria, which may over diagnose bacterial pneumonias that may be viral in origin or some other illnesses presenting as pneumonia. However for community-based intervention in third world countries this may be the best option. Also with the introduction of the community-based Lady Health Worker the WHO and UNICEF-sponsored integrated management of childhood illness (IMCI), such as pneumonias, re-emphasizes early case detection and appropriate case management of ARI that has proven to be effective in our rural settings.[67,68] Noorani and co-workers have shown that health care workers at 14 health centers managed 949 children, aged 2-59 months, with non-severe pneumonia.[68] Only 11.6% failed therapy with oral cotrimoxazole which is an acceptable treatment choice in view of the efficacy, cost and ease of use.

For a more scientific and evidence based recommendations we need to look at the likely pathogens encountered in children with pneumonias in Pakistan. However there is lack of data to make any firm conclusions. Butt *et al* looked at etiology and antimicrobial susceptibility pattern of bacterial community-acquired pneumonia in the Rawalpindi area.[69] Bacterial pathogens were isolated from 88 specimens (sputum, broncho-alveolar lavage fluid and tracheal aspirates) from adults and children. Most common isolates were *H. influenzae* (73%), *Moraxella catarrhalis* (*M. catarrhalis* 12%), *Strep. pneumoniae* (10%) and *H. parainfluenzae* (5%). Isolates of *H. influenzae* were generally sensitive to amoxicillin-clavulanic acid (88%)

and ceftriaxone (97%) where as 33% were resistant to chloramphenicol. All the isolates of *M. catarrhalis* were sensitive to amoxicillin-clavulanic acid. One isolate of *Strep. Pneumoniae* was resistant to penicillin, while 2 showed relative resistance. Thus an empirical treatment for community-acquired bacterial pneumonia with amoxicillin-clavulanic acid would suffice.[69]

Ashok *et al* from Islamabad presented another evidence for high resistant pattern for pathogens isolated from 868 samples (635 nasopharyngeal (NP) and 133 blood) of children with pneumonia (Table 1).[70] For cotrimoxazole MIC levels were > 1119 g/ml in 73% (43% fully resistant MIC>4 g/ml) and 70% for *Strep. Pneumoniae* from NP and blood isolates respectively. The MIC levels > 1119 g/ml of cotrimoxazole in NP and blood for *H. influenzae* isolates were 62% (20% fully resistant MIC > 4 g/ml) and 55% (2% fully resistant). Penicillin had MIC levels > 0.12 g/ml in 26% (2% fully resistant MIC > 2 g/ml) and 35% (3% fully resistant) for NP and blood isolates for *Strep. Pneumoniae*. The MIC levels > 8 g/ml for *Strep. Pneumoniae* for chloramphenicol in NP and blood isolates were 18% and 16% respectively. The MIC levels showed high in-vitro antimicrobial resistance to cotrimoxazole as compared to other antibiotics tested in blood and NP isolates making it a poor choice for children with pneumonia.[70]

Nizami *et al* measured the incidence of acute respiratory infections and burden of respiratory pathogens in children aged two months to five years in four periurban communities in Karachi.[71] A total of 1097/5884 children had pneumonia and severe pneumonia, with an incidence 440/1000 children per year for ARIs and 82/1000 children per year for pneumonias. *H. influenzae, Strep. pneumoniae* and *K. pneumoniae* were isolated from 10.9%, 3.7% and 8.5% of oropharyngeal swabs respectively. Extrapolating from the results of this study, the total number of cases of pneumonias in children aged less than five years in Pakistan was estimated to be 213,116 per year due to *H. influenzae*, and 71,864 per year due to *Strep. pneumoniae*. This is a huge disease burden. Hussain *et al* estimated the huge treatment costs for pneumonia, meningitis, and sepsis in health facilities in the Northern Areas of Pakistan.[72] The average cost of treatment was very high for hospitalized children.

Despite the lack of good and ample data for pneumonia pathogens the current recommendations of amoxicillin as first line therapy should be followed. Etiological diagnosis will make evidence-based recommendations meaningful. The preventive aspects such as improving nutrition, breast feeding, reducing indoor pollution, use of zinc, improving mass vaccination and addition of new vaccines for respiratory pathogens such as the *H. influenzae type b* and pneumococcal vaccines in our EPI schedule will likely have the most impact on reducing severe ARI and deaths from severe disease.

Meningitis

Acute bacterial meningitis is a common cause of significant morbidity and mortality in children. The etiology of bacterial meningitis in children in Pakistan is most probably the same as in the western literature reference.[73] Data on exact spectrum and resistance has been lacking. Here we will review some of the available and published data of bacterial meningitis, it's etiology and resistance pattern in children in Pakistan.

Most studies have not clearly delineated the etiologic agents or the culture data. Reliance has been on either cerebrospinal fluid gram stains or clinical response to antibiotics because of limited lab facilities. A prospective study of 112 children of epidemic meningococcal infection from Karachi by DS Akram *et al* in the early 90s showed that the penicillin was a cost-effective therapy with good response in 90% of the cases.[74] An observational study by Khichi *et al* involved 300 children of pyogenic meningitis, aged 2 months to 12 years, showed a high mortality rate of 10% (30/300).[75] Among the etiological microorganisms isolated from culture of CSF, only *Strep. pneumoniae* had statistically significant association with mortality. A retrospective of 200 consecutive children (mean age of 2.25 years) with meningitis from Mayo Hospital, Lahore were divided in two groups that received chloramphenicol along with either benzyl penicillin or ampicillin and cefotaxime, ceftriaxone or ceftazidime.[76] It showed that cure rate and complications were comparable between to two group but deaths were more in second group (14 vs. 5 respectively, $P < 0.05$). It meant that the traditional antibiotics benzyl penicillin and chloramphenicol were effective antibiotics for meningitis.

All other studies of etiology of meningitis show that *Strep. Pneumoniae, N. Meningitides* and *H. Influenzae* are the three most common causes of bacterial meningitis in our children and adults and can cause significant morbidity and mortality. [77-80] Limited resistance data from all these and above suggest that the empirical therapy with a third generation cephalosporin (or chloramphenicol) should be used. The use of vancomycin for empirical therapy for meningitis may not be warranted yet.

Infections in immune compromised children

Beyond neonatal period bacterial sepsis is uncommon in older children. Both community and nosocomial sepsis has been described. The most common agent for sepsis in infants and children in Pakistan is *Salmonella typhi* and other *Salmonella spp.* causing typhoidal fever that has been dealt in detail above. We will review some of the studies that have reported sepsis and bacteremia in mostly immunocompromised hosts. These studies may be difficult to interpret as mostly these are hospital-bases studies. Also both unusual and opportunistic organisms are included and may not be reflective of community acquired bacteremia and sepsis in healthy children.

Bhatti *et al* from Karachi reported on 153 isolates in 35 different *Enterobacteriaceae* (11.8%), *S. aureus* (9.1%) and *P. aeruginosa* (8.6%). Malnutrition is common in our communities. It has

been shown to be a risk factor for bacteremia due to gram negative organisms, such as *Enterobacteriaceae*, and death among hospitalized malnourished children with diarrhea.[84] Khan *et al* reported that sepsis was leading the cause of death in all age groups including children in the emergency room accounting for a total of 36% cases in a 2 year period.[85]

Management of both healthy and immunocompromised children with sepsis is a priority. Empiric antibiotics are usually broad spectrum and largely depend on severity, site and available local data. Most pediatric studies have not directly addressed this issue of choice of antibiotics. Some adult studies have given us some answers. Burney *et al* reported bacterial infections including bacteremia in febrile neutropenic patients with various malignancies.[86] A total of 127 bacteria were isolated from these patients (54% gram negative; 46% gram positive). *E. coli*, *P. aeruginosa*, *S. aureus*, *enterococcus* and *streptococci* were the commonly isolated organisms. *E. coli* exhibited a great degree of resistance to the commonly used antibiotics, such as pipericillin (70%), ofloxacin (50%) and aztreonam (50%). *Pseudomonas* and *klebsiella* also showed varying degree of resistance against these antibiotics. *S. aureus* and *S. epidermidis* were almost universally resistant to penicillins and showed a variable degree of resistance to other antibiotics too.[86]

Chaudhry *et al* from three hospitals in Lahore reported cause of septicemia among 364 patients.[87] Aerobic blood cultures were positive in 59%. *S. aureus* and *coagulase negative staphylococci (CONS)* were predominant among Gram-positive isolates while *Pseudomonas species*, *enterobacter cloacae* and *K. pneumoniae* were predominat gram-negative isolates. Fluoroquinolones (ofloxacin and ciprofloxacin) had good activity against both gram-positive and gram-negative organisms. Khan *et al* from 404 febrile neutropenic patients reported isolation of 124 bacterial organisms (positive blood culture 67%) from 96 patients.[88] *CONS* was reported as the most common gram-positive organism but was probably a skin contaminant. *E. coli* was the most commonly isolated gram-negative organism. There was emerging resistance to all commonly used broad-spectrum antibiotics, used in these immunocompromised patients, including imipenem, cloxacillin, vancomycin and amikacin.

These observations make empiric antibiotic choices difficult in all patients especially the immunocompromised and the severely sick. Physicians and pediatricians should rationally choose broad-spectrum antibiotic combination such as a cephalosporin, extended penicillin or a carbapenem with or without an aminoglycoside. Vancomycin would be added in these children with sepsis who have central line, are known colonizers or have prolong hospitalization or other risk factors for MRSA.

Urinary Tract Infections

Urinary tract infections (UTIs) in children are common in the first years of life and especially those with underlying congenital urinary tract infection.[89] There is some good data in Pakistan to support evidence based recommendations for management of UTIs (Table 1). In adults studies have shown that *E. coli* and *Klebsiella aerogenes* are the most common organisms causing UTI with changing and increasing antibiotic resistance to first line antibiotics.[90] Khan in his study of 400 cases of UTI highlighted that majority (85.5%) of organisms were due to gram-negative bacilli (77% *E. coli*, 14% *K. pneumoniae*, 5% *Proteus species* and 4% *P. aeruginosa*).[91] The overall resistance was high (ampicillin 62%, cotrimoxazole 65%, minocycline 56%, nalidixic acid 44%, norfloxacin 31%, Pipemidic acid 36%, ciprofloxacin 27%, gentamicin 44% and ceftriaxone 25%). For hospital-acquired catheter related urinary infections a shift to *enterococcus* species such as *enterococcus faecalis* has been documented.[92] Another study of mostly adult patients of 775 urine specimens (*E. coli* 51%, *Klebsiella spp* 16%, *P. aeruginosa* 9%) showed how some of first line antibiotics for UTI have lost their susceptibility.[93] Resistance of *E. coli* to different antibiotics was 7-70% and that of *Pseudomonas* isolates 3-69%..

Another study almost a decade ago of 32,722 urinary specimens (*E. coli* 53%) from Aga Khan University Hospital has shown an alarming resistance of *E. coli* against most antibiotics, particularly quinolones (Table 1).[94] More so that the increased utilization of quinolones correlated with increasing resistance over the years in all subspecialties including pediatrics (12 to 38% increased resistance). There was significant correlation between the increase in the incidence of ofloxacin resistant strains of *E. coli* and the ofloxacin utilization in the hospital. In pediatric population a cross-sectional study from Peshawar by Amin *et al* reported the bacterial spectrum and antibiotic sensitivity in 54 children aged 1 month - 12 years.[95] Common pathogens isolated were *E. coli* (57%), *Citrobacter* (17%) and *Proteus* (11%). There was good sensitivity for amikacin, gentamycin, cefotaxime and amoxicillin-clavulanic acid. A smaller Lahore based study from The Children's Hospital of 30 children, mean age 5.6 years, showed that *E. coli* was the most common organism (43%) followed by *klebsiella* (30%) and *pseudomonas* (17%).[96] Children with underlying structural anomalies were more susceptible to *pseudomonas*, *klebsiella* and other unusual opportunistic organisms.

A variety of commonly encountered uro-pathogens are reported in Pakistani children. These organisms have notoriously become much more resistant to common antibiotics. Choosing the right antibiotic(s) for community and hospital-acquired UTI need take into consideration many factors such as underlying structural anomalies, immunosuppression, hospital stay, local antibiogram patterns, prior UTIs and antibiotic use.

Skin, Soft Tissue Infections (SSTI) and Bone and Joint Infections

The commonest organisms responsible for SSTIs and bone and joint infections are *S. aureus* and *Strep. Pyogenes*. Few studies have been done on etiology and susceptibility of microorganisms

causing SSTIs and osteomyelitis in Pakistan particularly children. A prospective study of 100 patients (adults and children) with SSTI showed *S. aureus* (45%) as the commonest organisms with high incidence of resistance to penicillins, intermediate to quinolones and lowest among cephalosporin.[97] Malik *et al* reported the etiology of osteomyelitis of 150 patients (including children) from four hospitals in Lahore.[98] Interestingly isolatesincluded *Enterobacteriaceae* (32.8%), followed by *S. aureus* (29.5%), *P. aeruginosa* (15.5%), anaerobes (2.6%) and miscellaneous (19.3%). Susceptibility was not reported. Previous studies have reported a higher frequency of 37.5%[99] and 79%[100] of *S. aureus*. None were reported to have MRSA. However the gram-negative predominance and high resistance could be explained by the nosocomial acquired infections in some of these studies.

A total of 40 patients (including children, mean age 11 years) with septic arthritis from Peshawar had 82.5% culture yield of the synovial fluid.[101] *S. aureus* (57.5%) and *Strep. pneumoniae* (20%) were the major pathogens isolated. First generation cephalosporin, ampicillin–clavulanic acid combinations were the most effective antibiotics. Another study from Aga Khan of 39 children, including 6 neonates (mean age of 3.9 years), with septic arthritis of the hip was reported.[102] Blood culture was sent in all patients and was positive in 9 (23%) patients. It showed *S. aureus* commonest organism in blood cultures (4, 10.3%) and joint fluid cultures (28, 71.8%) but susceptibility was not reported.

In Pakistan the prevalence of MRSA will also determine the management of patients presenting with such infections. A study by Hafeez *et al* showed a high prevalence of 35.7% of MRSA isolates (448/1322 total) in patients in intensive care units and special care wards.[103] Resistance reported was ciprofloxacin (86.6%), erythromycin (85.5%) and gentamicin (81%). While vancomycin showed 100% susceptibility only fusidic acid with 21% was the other therapeutic option. Another hospital based study found a rate of 39% of *S. aureus* isolates (105/273).[104] The strains were fully (100%) susceptible to vancomycin and teicoplanin followed by fusidic acid (80% susceptible). The exact prevalence of community rate of MRSA carriage is unknown but is may increase in future. Only one study by Anwar *et al* in our general population has been highlighted MRSA carriage among general population.[105] Out of 1660 subjects (including children) who had nasal swabs a total of 246 (14.8%) were positive for *S. aureus* (nasal carriers). Of these 48 (19.5%) isolates were MRSA. Nasal carriage was significantly higher for the urban compared to the rural subjects ($p<0.05$).

In summary therapy for skin, bone and joint infections in pediatrics is dictated by local microbiologic data. The commonest organisms responsible are *S. aureus, Strep. pneumoniae* and sometimes other organisms such as gram negatives and *salmonella* should be considered as well especially in children with burns and immunocompromised. The burden of MRSA in invasive skin, bone and joint infections has not been much in Pakistani literature. However the presence of MRSA as a cause of infection at other sites indicates that it may also be responsible for skin, bone and joint infections. Specific therapy should be tailored according to culture results. Mostly anti-staphylococcal penicillin or a first generation cephalosporin for uncomplicated community acquired infection should suffice. Vancomycin may be warranted for those with risk factors for MRSA.

Malaria

One of the five major killers of childhood, malaria has received a lot of attention. It is estimated that malaria affects about 300 million people and causes more than a million deaths per year worldwide mostly infants, young children and pregnant women and most of them in Africa.[106] In Pakistan the estimates for malaria are high especially in endemic regions.[106,107] Based on active and passive case detection and malariometric survey of all districts of Sindh the Provincial Malaria Control Program has estimated the annual parasite incidence of 5.6-3.9 per 1000 population over a two year period.[107] These figures would be expected to show variation each year. The global rise of resistant malaria due to *Plasmodium (P.) falciparum* has also been reported in Pakistan. Estimates of choloroquine-resistance may account for more than 90% of malaria cases in many countries. In Pakistan these figures are reported to be 16-62% for *P. falciparum*.[108] Also 4- 25% of *P. falciparum* show resistance to sulfadoxine-pyrimethamine and several cases of delayed *P. falciparum* clearance have been observed in patients with malaria treated with quinine. We will now look at some of the pediatric data on malaria resistance in Pakistan.

Arain *et al* reported in-vivo choloroquine resistance in 80 children with *P. falciparum* malaria (Table 1).[109] Twenty-two (36.6%) were resistant to chloroquine. These resistant cases were treated with intravenous quinine but 5% resistance was also seen to quinine. Overall mortality was 3.7%. In a District Hospital in Sindh 406 children with malaria were seen.[110] Sixty-five percent had *P. falciparum*, 33% *P. vivax* and 2% had both. Approximately, 81% responded to choloroquine while 19% were non-responders. Choloroquine non-responders were treated with halofantrine, sulfadoxine-pyrimethamine or parenteral quinine. In the North West Frontier Province (now Khyber Pakhtunkhwa) there has also been reported resistance in 50 children from a Tehsil Headquarter Hospital.[111] Resistance to amodiaquine was found in 37.5% and to halofantrine 6.6%. In a large efficacy study of 200 children with malaria (62.5% *P. vivax*, 36% *P. falciparum*, 1.5% mixed infection) there was one third (41/125) RII resistance noted in *P. vivax* and only one case of *P. falciparum* RIII resistance.[112] In a study of 109 adults with *P. vivax* the efficacy of halofantrine was only 47% with a relapse rate of 3.7% making it a poor first line drug.[113] Khichi *et al* in an analytical study of 45 cases of neonatal malaria (30 congenital (<10 Days) and 15 acquired (11-28 days)) showed a high choloroquine resistance and mortality.[114] Using standard dose of choloroquine sulphate the rate of choloroquine resistance was 27% in congenital

Table 1. Resistance rates for common infections in chidren in Pakistan

Sites / Groups	No. of Children*, City	No. of isolates	Common pathogens (%)	Resistance (%)	Year of study	Ref.
Neonatal Infections	60, Karachi	60	*Klebsiella species* *Salmonella parathypi* *Group A Streptococcus*	Ampicillin and gentamicin (67%)	1986-9	10
	212, Karachi	212	*S. aureus* (30) *K. Pneumonia* (34) *Acinetobacter baumannii* (11) *E. coli* (11) *E. cloacae* (9)	MRSA (61%) Ampicillin/co-trimoxazole (90%) Gentamicin (90%) *K. pneumoniae* (60.9%) *Acinetobacter baumannii*: 3rd generation cephalosporins and ciprofloxacin (25-75%)	1997-9	11
	228, Lahore	233	*S. aureus* *E. Coli*	Cefotaxime ceftazidime, amikacin (34-80%) Ciprofloxacin (13-72%)	2003	12
	109, Karachi	109	*Enterococcus* *S. aureus* *Klebsiella spp.*	Ampicillin (80%) Cefotaxime (11-16%) Amikacin (0-10%)	92-94	13
	1003, Peshawar	1003	*E. coli* (36.6) *S. aureus* (29.5) *Pseudomonas* (22.4) *Klebsiella* (7.6) *Proteus* (3.8)	*E. coli* (23-93%) *S. aureus* (26-73%) *Pseudomonas* (23-96%) *Klebsiella* (6-82%) *Proteus* (16-70%)	1997-2000	14
	67, Peshawar	67	*E. coli* (80)	Ampicillin (79%), Ceftazidime (72%), Cefotaxime (55%), Gentamicin (43%), Tobramycin (34%), Imipenem (24%), Amikacin (22%), Fluoroquinolones (12%)	2003	16
	64, Karachi	64	*E. coli (*54) *K. pneumoniae (*21) *Enterobacter aerogenes (*16)	Maximum sensitivity to ceftazidime, aminoglycosides and ceftriaxone	2005	17
	319, Karachi	319	Gram-negative organisms (92%): *Enterobacter* (53) *Klebsiella* (22) *Pseudomonas* (21) *E. coli* (2), Gram-positive organisms (8%): *S. aureus* (70) *S. Pneumoniae* (17)	Gram-negative organisms: Ampicillin (83-100%), Cefotaxime (83-100%), Ceftazidime (73-100%), Imipenem (0-81%), ceftriaxone (66-100%) Gram-positive organisms: Amoxicillin-clavulanic acid (29-100%)	2004-5	18
	100, Karachi	100	*Klebsiella (*24) *S. aureus* (22) *Pseudomonas* (20) *Enterobacter* (9) *E. coli* (9)	Ampicillin (87%) Tobramycin (66%) Gentamicin (61%) Cefotaxime (65%)	2001-2	19
	62, Multan	62	*E. coli* (37), *Klebsiella* (10), *S. aureus* (32)	Ampicillin (100%) *E. coli* resistance: Cefotaxime (25%) Ceftazidime (32%) Imipenem (20%) Ciprofloxacin (48%)	2003-4	20
	78, Karachi	122	*Acinetobacter spp*	Pan-resistance (71%)	2003-8	122
Diarrheal Diseases	152, Lahore	152 stool cultures	*Shigella spp. (*19) *Campylobacter* (8), *Salmonella* (5)	*Shigella* isolates: nalidixic acid (0%), cotrimoxazole (93%), ampicillin (96%)	1990	27
	Karachi	193 stool samples	*Shigella flexneri* (58), *S. sonnei* (16), *S. boydii* (15), *S. dysenteriae* (11)	Ofloxacin (0%), ceftriaxone (0%), cotrimoxazole (88%), ampicillin (56%), nalidixic acid (39%)	2002-3	28
	Karachi	394 stool samples	*S. flexneri* (62), *S. sonnei* (18), *S. boydii* (11), *S. dysenteriae* (9)	Nalidixic acid (0%), co-trimoxazole (56-89%), ampicillin (4-87%)	2002-4	29
	886 adult and children,	888 stool	*V. cholerae*	Ofloxacin (0%), cotrimoxazole (63-100%),	1990-6	36

	Karachi	samples	serogroup O1 (64), serogroup O139 (36)	erythromycin (0-67%), nalidixic acid (>98%), tetracycline (91-100%), chloramphenicol (8-35%)		
	348, Karachi	348 stool samples	*V. cholerae Ogawa biotype Eltor* (86), *V. cholerae 0139* (14)	3rd Generation cephalosporins, ofloxacin, nalidixic acid, ampicillin and erythromycin (0%), tetracycline (0-83%), co-trimoxazole (100%)	1990-5	37
	212, Islamabad	212 isolates	*V. cholera (EIT or Ogawa)*	Ampicillin (7-100%), Nalidixic acid (0-61%), chloramphenicol (50-100%), tetracycline (93-100%), cotrimaxazole (95-100%), quinolones (0%), doxycycline (0%)	1994-9	38
	161, Karachi	161	*V. cholerae*	3rd generation cephalosporins and quinolones (0%), nalidixic acid (100%), chloramphenicol (14-18%), doxycycline (25-33%), cotrimaxazole (100%)	1998-2000	39
	Islamabad		*V. Cholera Eltor biotype Ogawa*	Nalidixic acid (100%), doxycycline, ofloxacin, ciprofloxacin and erythromycin (0%)		41
Typhoid	355, Karachi	355	*S. typhi*	First line drugs (ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole 20%)	1991	45
	100, Peshawar	100	*S. typhi*	Amoxicillin (82%), chloramphenicol (83%), cotrimaxazole (95%), MDR (18%), ofloxacin (100%), ciprofloxacin (98%), Cefotaxime (88%), ceftriaxone (86%)	1993-4	46
	76, Karachi	76	*S. typhi*	Amoxicillin and chloramphenicol (26%)	1993-4	47
	50, Peshawar	50 isolates	*S. typhi*	Amoxicillin, chloramphenicol and cotrimaxazole (90%), ciprofloxacin (0%), 3rd generation cephalosporin (57-79%)	1993-4	48
	Adults and children, Rawalpindi	2551 isolates	*S. typhi* (80), *S. paratyphi A* (20)	*S. typhi:* MDR (<10% in 1989 75% in 1995), fluoroquinolones or 3rd generation cephalosporins (0%), *S. paratyphi A:* Both the conventional and 2nd line drugs (0%)	1987-95	49
	109, Rawalpindi	109 isolates	*S. typhi*	MDR (72%)	1996	50
	876, Karachi	876 isolates	*S. typhi*	MDR (32%)	1996	51
	304, Karachi	304 isolates	*S. typhi* (82), *S. paratyphi A* or *B* (28)	Ampicillin (46%), chloramphenicol (39%), cotrimoxazole (45%), quinolones, and 3rd generation cephalosporins (0%)	1998-9	52
	Adults and children, Rawalpindi	140	*S. typhi* (73), *S. paratyphi* (27)	*S. typhi,* (45%) and *S. paratyphi (*47%) had a very high minimum inhibitory concentration's (MICs) of all the three conventional drugs (chloramphenicol, cotrimoxazole, ampicillin)	1998	53
	100, Karachi	95	*S. typhi* (95), *S. paratyphi A* (3), *S. paratyphi B* (2)	First line drugs (0%)	2003	54
	119, Islamabad	119	*S. typhi*	MDR (67%)	1990-3	55
	Adults and children, Rawalpindi	887 blood isolates	*S. typhi* (54) *S. typhi A* (46)	MDR strains: *S. typhi* decreased (80% to 13%), *S. paratyphi A* increased (14% to 44%, Fluoroquinolones (2.5%), 3rd generation cephalosporins (0%)	1996 vs 2003	56
	Adults and children, Rawalpindi ceftriaxone (0)%	333 blood isolates	*S. typhi* and *S. paratyphi A*	MDR (52%), ciprofloxacin, ofloxacin and	2001-2003	57
	217 adults and children Karachi	131	*S. typhi* (60), *S. paratyphi A* (33), *S. paratyphi B* (7)	Ciprofloxacin (4%), Ofloxacin (4%), Cephalosporins (<4%), amoxicillin, (96%), Co-trimoxazole (30%), MDR strains (62%)	2008-10	123
Pneumonia	2073, Pakistan		*Strep. Pneumoniae* (46%), *H. influenza* (36%)	Co-trimoxazole resistance: *Strep. Pneumoniae* (78%-80%) *H. influenzae* (59%-61%)	1991-3	62
	88 adults and children, Rawalpindi	88 blood isolates	*H. influenzae* (73), *M. catarrhalis* (12), *Strep. pneumoniae* (10), *H. parainfluenzae* (5)	*H. influenza*: Amoxicillin-clavulanic acid (12%), ceftriaxone (3%), chloramphenicol (33%), *M. catarrhalis:* Amoxicillin-clavulanic acid (0%), *Strep. Pneumoniae*: penicillin (33%)	2005	69
	834, Islamabad	868 samples	*Strep. Pneumoniae, H. influenza*	Cotrimoxazole: *Strep. Pneumoniae* (>70%), *H. influenza* (62%). Penicillin: *Strep. Pneumoniae*	2005	70

				(>26%), Chloramphenicol: *Strep. Pneumoniae* (>16%)		
Meningitis	112, Karachi	112	*N. meningitidis*	Penicillin (10%)	1991	74
Sepsis (neutropenic febrile pediatric patients)	35, Karachi	153 isolates	Gram negatives (53), gram positives (34)	Gram negatives (0-100%), gram positives (0-34%)	1990-6	81
UTI	Adults and children, Karachi	9892 samples	*E. coli* (52), *Klebsiella aerogenes* (9), *P. aeruginosa* (9)	Overall resistance: *E. coli* (5-35%), *Klebsiella aerogenes* (15-65%), *P. aeruginosa* (15-70%),	1990-97	90
	400 adults and children, Abbottabad	400 samples	Gram-negative bacilli: 86%, *E. coli* (77), *K. pneumoniae* (14), *Proteus spp.* (5), *P. aeruginosa* (4)	Overall resistance Ampicillin (62%), cotrimoxazole: (65%), minocycline (56%), nalidixic acid (44%), norfloxacin (21%), Pipemidic acid (36%), ciprofloxacin (27%), gentamicin (44%) ceftriaxone (25%)	2000	91
	775 adults and children, Gujranwala	775 samples	*E. coli* (51), *Klebsiella spp* (16), *P. aeruginosa* (9)	*E. coli*: Ofloxacin (7%), norfloxacin (10%), ceftriaxone (11%), nitrofurantion (16%), gentamicin (18%), cephradine (23%), cotrimoxazole (68%) and ampicillin (70%). *Pseudomonas* isolates: amikacin (3%), aztreonam (17%), ofloxacin (49%), norfloxacin (53%), tobramycin (67%) and gentamicin (69%)	2002	93
	Adults and children, Karachi	32,722 samples	*E. coli* (53)	Increasing ofloxacin resistance in all subspecialties including pediatrics (12 to 38%)	1995- 2002	94
	54, Peshawar		*E. coli* (57), *Citrobacter* (17) and *Proteus* (11)	Good sensitivity for amikacin, gentamicin, cefotaxime and amoxicillin-clavulanic acid	2003	95
SSTI	100 adults and children, Rawalpindi	100 isolates	*S. aureus* (45)	High incidence of resistance in penicillins, intermediate to quinolones and lowest among cephalosporin	2002-3	97
	Adults and children, Lahore	1322, isolates	*S. aureus*	*Staph aureus*: MRSA (35.7%), Ciprofloxacin (86.6%), erythromycin (85.5%), gentamicin (81%), vancomycin (0%), fusidic acid (21%)	1999-2002	103
	Adults and children, Islamabad	1310 isolates	*S. aureus* (20)	MRSA (39%), Vancomycin (0%), teicoplanin (0%), fusidic acid (20%)	2004-5	104
	1660 healthy subjects, Lahore	246, nasal swabs	*S. aureus* (14.8)	MRSA (19.5%)	2002-3	105
Septic arthritis	40 adults and children, Peshawar		*S. aureus* (57.5) and *Strep. pneumoniae* (20)	First generation cephalosporin, ampicillin–cloxacillin, ampicillin–clavulanic acid combinations were the most effective antibiotics	1996-7	101
Malaria	80, Jamshoro	80, Peripheral smears	*P. falciparum*	Choloroquine resistance (36.6%), quinine resistance (5%)	1994-5	109
	406, Mirpurkhas, Sindh	406, Peripheral smears	*P. falciparum* (65), *P. vivax* (33), mixed (2)	Choloroquine (19%)	1991-2	110
	50, Charsadda	50, Peripheral smears		Amodiaquine (37.5%), halofantrine (6.6%), quinine+ fansidar (0%)	2003	111
	200, Attock	200, Peripheral smears	*P. vivax* (62.5), P. *falciparum* (36), mixed (1.5)	RII resistance in *P. vivax* (33%), RIII resistance in *P. falciparum* (<1%)	2002-4	112
	45, neonatal malaria, Bahawalpur	45 Peripheral smears	Congenital (66), acquired (33)	Choloroquine resistance (27-34%)	2001-3	114
	81, Karachi	81 Peripheral smears	*P. falciparum* (57), mixed infection (32), *P. vivax* (11)	Quinine (17%)	2007-8	115
Tuberculosis	300 adults, Rawalpindi	158	≥ One drug (52.67%),	MDR (13.7%), rifampicin (24%), isoniazid (26.3%), streptomycin (28%), ethambutol (23.3%),	1995-8	117

			pyrazinamide (29.7%), Primary (12-20%), acquired (19-44%)		
88 adults, Rawalpindi	88 samples	*M. TB*	Single drug (15%), >1 drug (16%), all four first line drugs (5.6%)	2002-2	118
582 adults, Lahore	582 samples	*M. TB*	≥ One drug (53%), MDR (16%), rifampicin (26.6%), isoniazid (23.5%), streptomycin (19.5%), ethambutol (11.8%), pyrazinamide (29.7%) Primary (12-20%), acquired (19-44%)	2004	119
672 adults and children, Peshawar	672 sputum samples	*M. TB*	Overall (11.3%), streptomycin (5.4%), isoniazid (7.6%), rifampicin (2.2%), ethambutol (1.8%), pyrazinamide (3.3%), Primary MDR (1.8%)	2007	120
15343 adults and children, Karachi (multicenter study)	15343 samples	*M. TB*	Significant trend of resistance: Isoniazid (10-40%), rifampin (7-30%), pyrazinamide (0-30%), streptomycin (5-18%), ethambutol (1-18%), MDR (2-32%), XDR (<0.2%)	1999-2007	124

*Includes children only unless specified to include adults
UTI= urinary tract infections, SSTI= skin and soft tissue infections, *M. TB= mycobacterium tuberculosis*, *MDR*=multidrug resistant, *XDR*=Extensively drug resistant

and 34% in acquired group. The mortality was 17% and 13% in the two groups respectively. A recent Karachi study of severe malaria in 81 children reported quinine failure in 17%.[115]

There are reports of in-vivo malaria resistance in parts of Pakistan. These needs to be validated by in-vitro testing as well to make firm recommendations for appropriate management in Pakistani population.

Tuberculosis

Mycobacterium tuberculosis (M. TB) can have mono-drug or poly-drug resistance. Isolates that are resistant to both isoniazid (INH) and rifampin are called multi-drug resistance TB (MDR TB). WHO estimates there were about 489,139 (4.8% of Total) cases of MDR TB globally in 2006, mostly occurring in Russian Federation, China and India.[116] In Pakistan the estimate was 15,233 cases (5% of total).[116] Drug-resistant TB has emerged as a great threat to the control of TB in many parts of the world including Pakistan. It is commonly seen in (1) patients who take medications irregularly; (2) have defaulted during therapy; (3) have had previous treatment; (4) have co-infection with HIV; (5) and children with adult source case who has culture-proven resistant TB.

In Pakistan drug-resistant TB in pediatric population has not been studied so far. The reason is *M.TB* culture and susceptibilities are done infrequently in both adults and children (Table 1).[117-120] A pediatrician who suspects drug-resistant TB must try to know the susceptibility in the adult source case and also perform culture specimens of the child suspect. If strongly suspected physician should empirically treat for resistant TB according to resistant pattern in his region and as per WHO guidelines (Re-treatment Cases).[121]

Adult studies in Pakistan have showed an alarmingly high rate of MDR TB (2-32%).[117-120] Butt *et al* showed that among a total of 88 extrapulmonary *M. TB* mostly adult cases resistance to one drug was 15%, multi-drug resistance 16% and all four first line drug-resistance was 5.6%.[118] Rizwan et al. from Lahore in a large study of 582 TB culture positive cases compared resistant pattern among primary and acquired TB cases.[119] An alarming high resistance of 53% to any drug was noted, MDR was 16% while significantly higher among those with acquired cases. Also resistance was higher compared to there previous study of 1999.[117]

For every child with TB, culture and susceptibility should be known from the adult source case, if available.[121] It is also preferable that the child has AFB culture and susceptibility performed especially if

(i) the source case has drug-resistant TB;
(ii) those with extra pulmonary TB and extensive disease;
(iii) poor response to standard therapy.

The treatment of drug-resistant TB in children must be individualized according to available drug susceptibility information, available drugs and the patient's tolerance of the drugs. Treatment regimens must include two bactericidal drugs to which the organism is fully susceptible, and all treatment should be by DOTS, whenever possible. An expert in the management of TB must be consulted in cases of suspected and proven MDR TB.

Recent Literature 2009-12

Recent data not covered here relates to 2009-2012 period. Newer trends and higher resistance in neonatal sepsis,[122] typhoid,[123] TB[124] and malaria[125] are persistently being encountered. This only confirms that the problem of antibiotic resistance is out of control. Unless contributing factors such as antibiotic misuse[126] and poor infection control[127] are not tackled we will become helpless in treating even the most common infections highlighted in this article.

Major Findings and Recommendations

1. Available literature about the problem of resistance in children is not comprehensive.

2. Microbiologic methods for isolation of organisms may have differed in most studies.
3. Etiologic agents for different infections have showed secular and geographic variations over the last few decades.
4. Most organisms have shown increasing drug resistance with poor outcome.
5. The main clinical syndromes (neonatal sepsis, pneumonia, typhoid, UTI) have recorded newer resistance pattern and increase.
6. Major contribution to the increasing drug resistance include indiscriminate and overuse of antibiotics, inappropriate antibiotic selection, poor infection control practices or institutional antibiotic policies, substandard antibiotics in the market, etc.
7. Larger studies with robust data are needed to validate these findings and see newer trends for improving outcome of different infections.

Most common systemic infections and etiologic agents have been elucidated in the local literature. Despite the poor number and quality of data on pediatric infections and drug resistance, available data suggest that there is increasing drug resistant problem over last few decades. The use of antibiotics must be judicious to have greater impact on the rising microbial resistance. There is a greater need to have large studies that are done both at the community and all health care facilities to elucidate the extent of both burden and resistance of pediatric infections in Pakistan.

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ORIGINAL ARTICLE

Human Immunodeficiency Virus, Hepatitis B and C: Barbers knowledge and their Practices

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Abstract

Background
The rapid spread of Hepatitis B,C and Human Immunodeficiency Virus (HIV) is a serious global issue. Evidence suggests that razors and barber's scissors are risk factors for the transmission of these blood borne diseases. We assessed the knowledge and practices of barbers regarding transmission of these diseases in Karachi, Pakistan.

Methods
A cross sectional survey was conducted on barbers from July to August 2011 in Karachi Pakistan and barbers were interviewed to assess their knowledge regarding transmission of Hepatitis B,C and HIV, their source of knowledge and their practices pertaining to it.

Results
Significant association of correct knowledge was found with the charge of the haircut and the source of knowledge. There was no association of correct knowledge with the years of experience or the education level. Source of knowledge was electronic media and other people for most barbers. A total of only 39 barbers out of 120 were using disposable blades out of which 71% charged >200 Rs. per haircut. A significant association was observed between knowledge regarding the spread of these viruses and the charges taken. Barbers who were charging mediocre amount were found to be more knowledgeable regarding HBV & HCV as compared to those charging less than 50 rupees and higher than 200 rupees. Whereas knowledge regarding HIV was better in barbers charging higher amount of money.

Conclusions
The level of knowledge among barbers who charge mediocre and those who acquired the knowledge through the electronic media was found to be better than their peers. Future interventions focused on creating awareness should be based on electronic media.

Keywords
Barbers, HIV, AIDS, HBV, HCV, Razors, Public health

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Introduction

Over 2 billion people throughout the world, are infected with HBV,[1] and around 150 million live with chronically infected HCV,[2] the number increasing by 3 to 4 million every year.[2] The national program for control and prevention of hepatitis reports 19 million people suffering from hepatitis and 3-4% of Pakistani's are carriers of HBV, while another 5-6% are carriers of HCV.[3] In addition, HIV has an estimated 97400 cases in Pakistan as of 2009.[4] The acute and chronic morbidity and mortality of these blood borne diseases is humungous, imposing substantial burden on the national economy and families of the infected individuals due to rising cost of management and health care.[5] The escalating burden of the blood borne diseases warrants an urgent public health response.

Reuse of unsterile medical injection,[6] blood transfusion,[7] vertical transmission,[8] unsafe sexual activities,[9] tattooing[10] and sharing of razors[1] are important factors associated with HBV, HCV and HIV transmission.[9] HBV and HCV have also been implicated as an occupational hazard in barber shops, razor blades being the key risk factor.[12, 13] In Turkey, 39.8% of barbers were found to be HBV positive.[12] In addition to the employees, the customers are also under the risk of transmission if decontamination of working equipment, disinfection and sterilization, disposal of used blades are not practiced.[15] In Italy, a haircut imposes a risk of 1.7% for HBV and 1.8% for HCV. In Pakistan, studies recognize that daily facial and armpit shaving conducted by the barbers is a risk factor for transmission of HBV and HCV,[14] whereas to date no such study has been done regarding HIV in similar context in Pakistan.

According to recent studies barbers have low awareness about these diseases and the risk of transmission of infected agents by reuse of razors and scissors.[12] In Pakistan, the prevalence of shaving by barbers is between 39-49%.[10] Under such conditions it becomes important to evaluate the understanding of the barbers about diseases that are closely linked to their profession. Assessment of knowledge and practices of barbers may help to guide appropriate prevention and intervention strategies. However, to date only a few studies have evaluated the perception and practice of barbers in Pakistan. We therefore conducted this study to assess the knowledge and practice of the barbers of Karachi, regarding HBV, HCV and HIV.

Methodology

A cross-sectional survey was carried out on barbers working in Karachi between July to August 2011. In this pilot study a total of 120 male barber-shops were selected in Karachi from 8 localities through convenience sampling. The criteria of inclusion included barbers of all age groups who were working in Karachi irrespective of their years of experience. We excluded all those barbers who were not willing to participate or those absent at the time of data collection. The survey included barber shops from low, middle and high income areas. After explaining the purpose of study, a verbal consent was taken for interviewing them about their knowledge and practices. A pre-tested, structured questionnaire, filled by the investigator, was used to determine the knowledge of barbers regarding the spread and prevention of Hepatitis B & C, and HIV/AIDS. Barbers were inquired regarding their practices in the profession, cleanliness, instruments and themselves. Other questions asked included; source of knowledge regarding each disease, education, years of experience and charges for hair cutting. For the purpose of our analysis we categorized the charges as 'High Charges', (>200Rs), 'Moderate Charges', (b/w 50-200 Rs), and'Low Charges" (<50 Rs). Years of experience was categorized as less than 5 years experience, between 5-10 years and greater than 10 years. Data was entered and analyzed in SPSS version 17. Descriptive statistics was used to calculate frequencies and percentages of knowledge and practices. Associations between categorical variables were determined by using chi-square test. A p – value less than 0.05 was considered statistically significant.

Results

A total of 120 barbers participated in the study that focused on the knowledge and practices of barbers regarding Hepatitis B, C, and HIV. Electronic media served as the medium for conveying knowledge for 55 (45%) barbers and another 55 (45%) got it from clients and other people as shown in Table 1.

Barbers who charged more had better practices. Practices regarding use of hygienic measures while using instruments were also significantly associated with their charges. (Graph1).

Regarding knowledge, barbers were cognizant irrespective of their charges. Questions on knowledge of the diseases to the charges are shown in Table 3. Association between years of experience and practices of barbers has been shown in Table 2.

Discussion

This study was conducted to assess the knowledge of barbers regarding HBV, HCV and HIV and to demonstrate their practices that may contribute to disease transmission. The level of knowledge of barbers was better as compared to others studies.[11, 5] Overall the knowledge was much better in barbers entertaining clients from higher socioeconomic class with higher charges. People from high socioeconomic class were presumably better aware of infectious diseases; hence we presume that their knowledge served as a conduit to actuate the knowledge of their barbers. Another possibility is that the barbers with higher charges tend to have television sets for the entertainment of clients and it served as a source of education for barbers as well.[15] Majority of the barbers reported television as their source of

Table 1: Socio-demographic Characteristics of the barbers who participated in the study

Characteristics	n	%
Age of the barber		
15-20yrs	9	7.5
21-30yrs	67	55.8
31-40yrs	27	22.5
>40yrs	17	14.2
Education level of the barber		
No education	5	4.2
Primary	37	30.8
Secondary	50	41.7
Graduate	20	16.7
Madressah	8	6.7
Experience of the barber		
<5yrs	43	35.8
5yrs-10yrs	30	25
>10yrs	47	39.2
Charges of the haircut		
<Rs.50	26	21.7
Rs.50-Rs.100	63	52.5
>Rs.200	31	25.8
Source of knowledge on the disease		
Electronic Media	55	45.8
Print Media	7	5.8
People	55	45.8
Other	3	2.5

Graph 1: Association between charges taken and practices of barbers

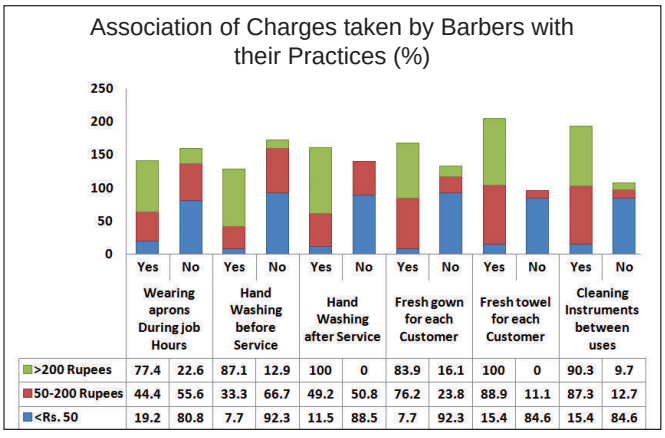

Table 2: Association between years of experience and practices of barbers for prevention of hepatitis B, C and HIV

		Years of experience						*P*-Value
		<5yrs (n=43)		5-10 years (n=30)		>10 years (n=47)		
		n	%	n	%	n	%	
Wearing aprons during job hours	**Yes**	19	44.2	15	50	23	48.9	0.859
	No	24	55.8	15	50	24	51.1	
Hand washing before service	**Yes**	14	32.6	8	26.7	28	59.6	**0.005**
	No	29	67.4	22	73.3	19	40.4	
Hand washing after service	**Yes**	21	48.8	12	40	32	68.1	**0.037**
	No	22	51.2	18	60	15	31.9	
Fresh gown for each customer	**Yes**	26	60.5	21	70	29	61.7	0.677
	No	17	39.5	9	30	18	38.3	
Fresh towel for each customer	**Yes**	29	67.4	22	73.3	40	85.1	0.138
	No	14	32.6	8	26.7	7	14.9	
Cleaning of instruments between uses	**Yes**	27	62.8	24	80	36	76.6	0.194
	No	16	37.2	6	20	11	23.4	
Disinfect instruments	**Yes**	13	30.2	9	30	24	51.1	0.071
	No	30	69.8	21	70	23	48.9	
Uses disposable blades	**Yes**	15	34.9	7	23.3	17	36.2	0.461
	No	28	65.1	23	76.7	30	83.8	

knowledge as opposed to newspaper which contributed to only 6% of the barber's knowledge. A similar pattern of rising trend of watching television for information and entertainment was also seen in one of the studies conducted in Rawalpindi where 80% of the barbers interviewed, watched television and considered it to be their primary source of information, thus emphasizing on the importance of electronic media on creating awareness of HIV and hepatitis amongst barbers.

Interestingly, the years of experience and level of education had no impact on knowledge. The reason for this might be that the education curriculum focuses on basic sciences rather than stressing on awareness of knowledge, pattern and transmission of the diseases currently prevalent in the community. Incorporation of the knowledge of infectious diseases in primary or secondary level education will prove valuable in controlling the spread of infectious diseases in our society. Reuse of blades is implicated in the transmission of the blood borne pathogens from person to person due to contamination of razors by micro trauma during shaving. The chance of transmission correlates with the frequency of reuse. Although mass campaigns have been carried out by different organizations regarding the hazards of reusing blades only about one third of barbers surveyed were changing blades after every customer. The results of this study are more or less similar to studies conducted in Gujarat, Rawalpindi and Islamabad,[11, 5] as they reported about 50% reuse of blades. This practice was similar in barbers of different demographic variations. The reason for not following this practice vigilantly seems to be because of insufficiency of knowledge. Barbers do know the name of the diseases and that they are deadly and infectious but they don't really know what these diseases actually are and how and what spreads them. These gaps in knowledge have been filled in by misconceptions and myths, which need to be attended to in order for barbers to carry out safe and healthy practices. Often the barbers themselves are accidently exposed to the blood of clients by cuts from scissors and blades. Apart from the reuse of razors, the common practice of throwing used razors openly possesses an additional threat to transmission to the garbage handlers as they linger in trash cans, scanning for metals, a practice seen widely all across Pakistan.[16]

The main limitation in our study was that our sample size was

Table 3: Association between charges taken and knowledge of barbers regarding Hepatitis B, C and HIV

			Charges taken for services						*P*-Value
			<50 rupees (n=26)		50-200 rupees (n=26)		>200 rupees (n=31)		
			n	%	n	%	n	%	
HEP B & C	Do you know about Hepatitis B & C	**Yes**	25	96	52	82.5	29	93.5	0.11
		No	1	4	11	17.5	2	6.5	
	Is it related to your profession	**Yes**	6	23	28	44.4	5	16	**0.002**
		No	19	73	24	38.1	24	77.4	
		Don't Know	1	4	11	17.5	2	6.6	
	How is it Spread	**Airborne**	0	0	1	1.6	0	0	**<0.001**
		Direct	2	7.7	24	38.1	2	6.5	
		Blood Borne	3	11.5	26	41.3	8	25.8	
		Don't Know	21	80.8	12	19	21	67.7	
	How you can prevent its spread	**Change Blades**	4	15.4	27	43	10	32	**<0.001**
		Change Linen	1	3.8	1	1.6	0	0	
		Wash Hands	1	3.8	22	35	19	61	
		Don't Know	20	77	13	20.4	2	7	
HIV	Do you know about HIV	**Yes**	24	92	56	88.9	30	96.8	0.425
		No	2	8	7	11.1	1	3.2	
	Is it related to your profession	**Yes**	5	19.2	43	68.3	28	90.3	**<0.001**
		No	19	73.1	3	20.6	2	6.5	
		Don't Know	2	7.7	7	11.1	1	3.2	
	How is it Spread	**Airborne**	0	0	0	0	1	3.2	**<0.001**
		Direct	3	11.5	44	69.8	27	87.1	
		Blood Borne	2	7.7	5	8	2	6.5	
		Don't Know	21	80.8	14	22.2	1	3.2	
	How you can prevent its spread	**Change Blades**	3	11.5	47	74.6	29	93.6	**<0.001**
		Change Linen	0	0	2	3.2	0	0	
		Wash Hands	19	73.1	2	3.2	1	3.2	
		Don't Know	4	15.4	12	19	1	3.2	

small and the method of data collection was convenience sampling that may have resulted in selection bias. Procedures like circumcision and other minor surgical procedures conducted by some barbers were not covered. Strengths of our study are that we included all barbers working from shops to roadside and conducted face to face interview. We not only interviewed them to find out about their knowledge and practices but also to figure out their source of information. We did not find any study conducted in Karachi on this issue. The increasing prevalence of these communicable diseases is a public health problem and requires multifaceted solutions.

Our study results can be beneficial in designing public health interventions. The rising costs entails more expenses required for maintenance of good hygiene practices, proper disinfection of instruments and disposal of waste. But these factors can only be taken into account where the barbers are taking better remuneration for their services. A large scale study is required to assess the different variables playing part in the spread of HBV, HCV and HIV. Laws should be implemented and acted upon for barbers to minimize the impact of the disease and its associated costs. Based on the results of this study policy makers should use the electronic media, to influence the current trends of knowledge and practices among barbers.[16]

Conclusion

Knowledge and awareness of barbers about hepatitis B, C and HIV is very low. Awareness sessions with targeted messages and programs in media campaigns and interventions for health education and regulation of barber's practices might help to enhance knowledge among barbers. An in-depth analysis of behaviors and determinants of practices can have a more

profound effect on designing specific interventions for barbers.

Authors' Contribution

MA carried out the literature search, helped in collecting data, did data entry and analyses and participated in the sequence alignment and drafting of the manuscript. BS helped in literature search, helped in collecting data, did data entry and analyses and carried out sequence alignment and drafting manuscript. SHD edited the final manuscript, did the analysis and wrote the results. OR participated in the design of the study and helped draft the manuscript.

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Compliance of Medicine Residents with 6-Hour Sepsis Bundle at a Tertiary Care Center

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Abstract

Objective
To determine the frequency of medicine residents' compliance with 6-hour sepsis bundle in patients with severe sepsis at the Aga Khan University Hospital

Methods
Cross-sectional study, conducted at the emergency room and medical wards of a tertiary care university hospital. The study was conducted from April to October, 2009. Sixty seven patients with severe sepsis and 67 medicine residents (postgraduate years 3 and 4) meeting the inclusion criteria were enrolled in the study after informed consent. A checklist was used to document whether all tasks of 6-hour sepsis bundle were undertaken and completed within 6 hours of making a diagnosis of severe sepsis.

Results
Overall residents' compliance with 6-hour sepsis bundle was 11.9%. Out of the 67 patients of severe sepsis, serum lactate was measured in 14 (20.9%) patient, blood culture before antibiotics was obtained in 38(56.7%) patients; 53(79.1%) patients received antibiotics within 3 hour of presentation to the emergency room and 1 hour of their diagnosis of severe sepsis in the ward. Initial fluid resuscitation was completed in 65(97%) patients. If the mean arterial pressure (MAP) remained less than 65mmHg despite adequate initial fluid resuscitation, vasopressors of choice were initiated in 55 (82.1%) cases. Central venous pressure of =8 mmHg was achieved in 53(79%) patients after adequate fluid resuscitation. Blood transfusion to target hemoglobin (Hb) of 7-9g/dl was given to 59(88.1%) patients.

Conclusion
Hospital mortality from severe sepsis can be reduced by enhancing compliance with evidence-based interventions through adoption of simple strategies which are relevant to our local problems and needs.

Introduction

Infection in hospitals continues to be a major concern all over the world.[1] Severe sepsis is an infection-induced syndrome resulting in a systemic inflammatory response that is complicated by dysfunction of at least one organ system. In the developed world, severe sepsis accounts for 1in 5 admissions to intensive care unit (ICU) andis the leading cause of death in the non-coronary ICU.[2] Sepsis is one of the most prevalent diseases and one of the main causes of death among hospitalized patients[3]. More than 18 million cases of severe sepsis occur worldwide each year accounting for 135,000 deaths in Europe and 215,000 deaths in the US.[3] Severe sepsis is associated with poor outcome and mortality rates as high as30% to 50% for severe sepsis and 50% to 60% for septic shock or 500,000 deaths per year worldwide.[4] The number of severe sepsis cases is expected to grow at a rate of 1.5% per annum from the current annual incidence of 3.0 cases per 1,000 of the population[3]. Sepsis progressing to septic shock with multiorgan failure is one of the leading causesof death in patients presenting to tertiary care Hospitals in Karachi. From a retrospective review of medical record, we have reported a mortality of 32-60% for sepsis and 40-80% for septic shock from The Aga Khan University (AKU), which is higher than that reported internationally.[5] Whether this observation is because of late recognition and inadequate management or because of genetic and immunological make-up of our population is the subject of another study.

In recent years there have been unprecedented advances in the understanding of epidemiology pathophysiology, and treatment of sepsis syndrome.[6] This work has culminated in several clinical trials demonstrating the efficacy of targeted interventions to improve sepsis-related outcomes. These interventions include not only novel therapeutic agents but also treatments directed at improving the way more traditional therapy is delivered, such as early resuscitation. A landmark study reported in New England Journal of Medicine in 2001 demonstrated that mortality from sepsis could be reduced by 16% with a protocol known as early goal-directed therapy (EGDT).[7] Unfortunately the gaps between evidence and practice are enormous.[8] Indeed, most of the available data suggests that results of clinical trials and observational studies have not changed clinical practice in sepsis care. Few emergency departments have implemented protocols for early resuscitation of patients with severe sepsis but delayed and/or inappropriate antibiotic administration remains common. Recent evidence suggests that grouping care practices together into "bundles" is an effective method to

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improve outcomes for complex diseases such as catheter-related bloodstream infections, ventilator-associated pneumonia, cardiac arrest and even sepsis.[9] The Surviving Sepsis Campaign group has introduced sepsis care bundles (6-hour sepsis and 24-sepsis bundles) into clinical practice.[10]

Compliance with application of sepsis bundle protocol has dramatically reduced mortality rate at various centers worldwide. In one study, the rate of compliance with 6-hour sepsis bundle was 52% and there was remarkable reduction in hospital mortality rate in patients who received 6-hour sepsis bundle as compared to those who did not receive it (29% versus 55%).[1]

The 6-hour sepsis bundle is the most vital initial resuscitation bundle that lists the tasks that should begin immediately upon diagnosis and must be accomplished by the attending physicians within the first 6 hours of presentation of a patient with severe sepsis either in emergency department, hospital units or ICU. The goal is to perform all the indicated tasks 100% of the time, within the first 6 hours of identification of severe sepsis.

In view of high sepsis-related mortality, sepsis bundles were introduced at AKUH in 2008-2009. This study was conducted to assess first-line physicians' (i.e. residents') compliance with the 6-hour sepsis bundle.

Materials and Methods

A Cross-sectional study was conducted over a period of 6 months from April to October, 2009. Data was collected in the emergency room and medical wards of a tertiary care university hospital (AKU). The study was initiated soon after implementation of sepsis bundles at the hospital.

Sepsis and septic shock were diagnosed as per the Society of Critical Care Medicine (SCCM) guidelines,[11] which state that patients with sepsis have a documented bacteremia together with any two of the following signs or symptoms: a) white blood cell count <4000 and >10,000 b) respiratory rate of >35 b/min or a PaCO2 <32 mmHg and c) temperature >37.5 degrees Celsius or <34 degrees Celsius. Patients who developed septic shock were defined by a mean arterial pressure of <60 mm Hg or hemodynamic instability.

A sample size of 67 instances of severe sepsis and/or septic shock was calculated assuming the proportion of compliance (P) with 6-hour sepsis bundle as =52%[1,] margin of error (d) =12%, confidence level=95%. Instances were captured through non-probability, purposive sampling.

These cases were managed by 67 medicine residents (postgraduate years 3 and 4) who first encountered the patients in the Emergency Room (ER) or on medical wards or intensive care unit. Informed consentwas taken from the patients or their next of kin and from the residents. A checklist was used to document whether all the tasks of 6-hour sepsis bundle were undertaken and completed within 6 hours of making the diagnosis of severe sepsis and/or septic shock.We used a hemoglobin target of 7to 9 g/dl instead of hematocrit = 30%, and used remaining hypotension after fluid resuscitation for threshold of inotropes instead of central venous oxygen saturation (ScVO2), as described by Gao *et al*.[1]

Subjects of either gender, >16 years of age with a diagnosis of severe sepsis and/ or septic shock were included. Subjects with Autoimmune disorders, pancreatitis, vacuities, burns and recent surgery were excluded.

The authors validated the diagnosis of severe sepsis/septic shock in every case and observed whether all tasks of 6-hour sepsis bundle were taken and completed within 6 hours by the residents. The tasks included: measurement of serum lactate level, obtaining blood cultures before administration of antibiotics, administration of broad spectrum antibiotics within 3 hours of ER admission and 1 hour for non-ER ICU admission, immediate administration of fluids (20-40ml/kg), administration of vasopressors formean arterial pressure (MAP) of <65 despite adequate fluid resuscitation (20-40ml/kg), blood transfusion to target hemoglobin of 7-9g/dl.

A 'yes' was markedon the checklist if the task had been executed stepwise as above by the resident within the first 6-hours after time '0' (diagnosis of severe sepsis); 'no' was marked otherwise. Compliance was labeled as present if all the tasks of 6-hour sepsis bundle protocol were carried out and completed within 6-hours by the residents from time of diagnosis of severe sepsis and compliance was absent if any of the tasks of 6-hour sepsis bundle had not been executed.

SPSS-version 10.0 was used for statistical data analysis. Frequencies and percentages were computed for gender,residents'compliance with 6-hour sepsis bundle and stratification on the basis of level of residency(postgraduate year),age,gender, and the type of postgraduate training (Fellowship of College of Physicians & Surgeons Pakistan (FCPS) or Membership of Royal College of Physicians (MRCP))the residents were enrolled in. Ethical approval for this study was obtained from The Aga Khan University Ethical Review Committee

Results

Patients' characteristics

Mean age of patients was 53.15 +/- 17.98 (18-86). Out of 67 patients 42(62.7%) and 25(37.3%) were male and female respectively. 61(91%) patients were diagnosed having severe sepsis in emergency department as compared to 6(9%) patients who were diagnosed in the ward.

Physicians' characteristics

Mean age of physicians was 31.58+/-1.60.43(64.2%) and 24(35.8%) were male and female physicians.For postgraduate

year, 46(68.7%) and 21(31.3%) physicians were in 4th (fourth) year and 3rd (third) year of their residency training respectively.

Compliance with 6-hour sepsis bundle

Overall physician's compliance with 6-hour sepsis bundle was 11.9%. Out of the 67 patients, within the first 6-hours after their diagnosis of severe sepsis, serum lactate was measured in 14 (20.9%) patient, blood culture before antibiotics was obtained in 38 (56.7%) patients, and 53 (79.1%) patients received antibiotics within 3 hour of presentation to emergency department and 1 hour of their diagnosis of severe sepsis in the ward. Initial fluid resuscitation was completed in 65(97%) of the patients. If mean arterial pressure (MAP) remained less than 65mmHg despite adequate initial fluid resuscitation, vasopressor of choice was initiated in 55 (82.1%). Central venous pressure of ≥8 mmHg was achieved in 53(79. %) patients after adequate fluid resuscitation. 59(88.1%) were those patients in whom either inotrope was used or blood transfusion to target hemoglobin (Hb.) of 7-9g/dl was given. All the elements of 6- hour sepsis bundle were received by 8 (11.9%) patients diagnosed to have severe sepsis.

Discussion

It has been established beyond doubt that sepsis bundles improve survival by improving the way sepsis treatment is delivered.[12,13,14] Therefore, it is reasonable to expect that hospitals would design strategies to ensure bundled care for all cases of severe sepsis. However, translating clinical evidence into practice remains a big challenge.[15] and there remains a wide gap between what is known and what is done.[16]

Bundled care for management of severe sepsis and for prevention of catheter-associated blood stream infections and ventilator-associated pneumonia has been introduced over the last few monthsat the Aga Khan University Hospital. Introduction of sepsis bundle was preceded by training sessions for staff and residents. However, our finding of low compliance with 6 hour sepsis bundle is not unexpected because most implementation strategies world-wide, fail to address barriers to implementation adequately."Patients receive recommended therapies only half of the time".[15] Developing guidelines and protocols, making them available, educating clinicians and advocating adherence have been repeatedly shown to be insufficient to change physician behavior, [17-20] as is evident from our study as well. "Patients are exposed to harm not only through medical errors but also by physicians' failure to adhere to evidence-based best practices".[15]

Low physician compliance (adherence) to SSC (Surviving Sepsis Campaign) recommendations of 6-hour sepsis bundle has also been reported in other studies. Ferrer R *et al* [21]prospectively evaluated the impact of an educational program on guideline compliance and mortality in patients with severe sepsis and found poor adherence to SSC recommendations at baseline. Compliance with all resuscitations measures of 6-hour sepsis bundle at baseline was only 5.3% as compared to our study (11.9% adherence with all elements of 6-hour sepsis bundle). Theyalso reported that the twoprocess-of-careswhich showed compliance higher than 50% at baseline weredrawing of blood cultures before antibiotics (54.4%) and early administration of broad spectrum antibiotics (66.5%). Comparing these two processes of care to our study, we also found compliance higher than 50% compliance in antibiotic usage as well as drawing of blood cultures before antibiotics (79.1% and 56.7% respectively). Chen QH et al [22] have clearly shown that compliance with sepsis bundles was low in training phase and the compliance increased after training. Compliance with 6-hour EGDT was 19.6% in the training phase and increased to 55.1% after training. Nguyen *et at*[9] found a progressive improvement from the baseline phase, at zero (0%) percentage compliance, to the end of QI (quality improvement) phase, at 51.2%. In that study baseline compliance with antibiotic usage was high (89.2%); otherwise adherence to early goal directed therapy was poor (8.1%) at baseline. Gao *et al*[1] found better compliance rates in two teaching hospitals in England. They prospectively observed compliance with a modified SSC 6-hour sepsis bundle at two teaching hospitals in the UK, incorporating hemoglobin target 7-9g/dl and persistent hypotension after fluid resuscitation instead of ScVO2 (central venous oxygen saturation) as a threshold for starting inotropic therapy. They found 52% compliance with 6-hour sepsis bundle. Compliance with guidelines for patients with severe sepsis at their first 6-hours of stay at the Emergency Department was poor.[23]

Regarding the evaluation of the individual elements of 6-hour sepsis bundle, our study has revealed that compliance with the measurement of serum lactate (20.9%) was very poor. This is not surprising because most studies have shown poor baseline compliance with this element of 6-hour sepsis bundle; [1]others have reported compliance of 12.5%.[23] and 16.7%[24] respectively. Compliance significantly increased to 78.3% after the application of standardized hospital order set for the management of patients with septic shock.[24]

Our compliance with the practice of obtaining blood culture before antibiotics was comparable with other studies. Blood cultures were drawn before antibiotics in 56.3% of patients with severe sepsis in our study. Ferrer R *et al* [21] reported compliance of 54.4% in pre-intervention group versus 62.4% in the post-intervention group. Others have also reported high compliance with this practice.[16, 24]Antibiotic administrations within 3 hours of arrival in the emergency room was noted in 60.0% of patients and 86.7% in the before-after study of a standardized hospital order set groups respectively.[24]

Compliance with the element of fluid resuscitation in our study was 97%. Micek ST *et al*[24] had found only 58.3% and 88.3% compliance with 20 ml/kg fluid resuscitation before vasopressors before and after the application of set hospital order respectively. Ferrer R *et al* [21] reported 40.9% compliance with fluid resuscitationin the preintervention cohort and 46.7% compliance

in the post intervention cohort. Compliance of our residents was better when compared to other studies.[23]

Use of vasopressors after fluid resuscitation to maintain mean arterial pressure (MAP) ≥ 65 mmHg, was also consistent and was noted in 82.1% of patients with severe sepsis and septic shock, whereas a much lower compliance (40.9%) has been reported earlier.[21] Jose M *et al* [23] had shown 43.3% of patients with septic shock required vasopressor therapy. Physcians'Compliance with achievement of central venous pressure (CVP) ≥ 8 mmHg was found to be 79.1% in our study. In the study done in Spanish ICUs[21] very few patients had undergone CVP monitoring and adequate CVP ≥8mmHg was achieved in 21.4% and 26.7% in the preintervention and post intervention groups respectively.

While improving patient care may seem to be an insurmountable task, it has been shown that efforts to translate research into practice are more effective when coupled with efforts to improve patient safety culture and teamwork. The implementation framework for improving culture and teamwork is known as the Comprehensive Unit-Based Safety Program (CUSP). Additionally, the Translating Evidence Into Practice (TRIP) framework has been proposed to improve patient care by implementing best-practice guidelines, identifying barriers to implementing these practices, creating measures to evaluate the efficacy of interventions, and reorganizing work to ensure that all patients who should receive the evidence-based practice actually do.

The best opportunity to improve patient outcomes in the future may come not just from discovering new treatments but also from learning how to deliver existing effective therapies.[25]

In Pakistan, delivery of health care is not uniform. Even at a single institution, practices vary from unit to unit and from individual to individual. In order to improve outcomes of our patients with sepsis (and other treatable conditions), even in resource poor settings, it is imperative that teaching and training of postgraduate doctors are up-to date and evidence-based and local barriers to implementation, both unit-based and institution-wide, are identified and addressed, not once but repeatedly to achieve and maintain appropriate outcomes.

Our study has the limitation of reporting only the frequency of compliance with the 6-hour sepsis bundle in patients with severe sepsis and not the outcome in terms mortality and we have shown that adherence to sepsis bundles guidelines was low in our emergency room and wards.

Conclusions and recommendations

The overall baseline compliance with 6-hour sepsis bundle in this study was poor but compliance with few individual elements of 6-hour sepsis bundle was consistent. Compliance with these evidence-based sepsis bundles needs extensive and intensive educational program and training of first interacting physicians' i.e. residents or postgraduate trainees, for the implementation of actions which have been shown to reduce mortality. Efforts to mitigate the hospital mortality from severe sepsis should focus on enhancing the compliance with these evidence-based interventions through internationally proven strategies after adaptation to our local circumstances.

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Neonatal Tetanus Elimination – A milestone yet far away.

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Approximately a million cases of tetanus are estimated to occur worldwide each year, with 300,000 to 500,000 deaths, while neonatal tetanus (NT) accounted for approximately 59,000 deaths in 2008.[1] There is steep decline in the NT mortality to 92% in 2010 compared with 1988, with exception of only 34 countries where maternal and neonatal tetanus has not been eliminated yet.[2]

It has been recognized that neonatal health is closely associated with maternal morbidity so improving maternal health and immunization can prevent the neonatal and early infancy diseases. This point has led to many antenatal interventions including tetanus immunizations in pregnancy and child bearing age. Tetanus was recognized in 1989 as a major health problem mainly affecting neonates. Pakistan is among those countries where NT incidence and case fatality rates were high. Tetanus accounts for 18-38% and 17-22% of all neonatal and infant deaths respectively. However the situation is not alarming as the incidence has decreased from 0.90/1000 live births (LB) in 1994 to 0.18/1000 LB in 2003.[3]

Despite the decreased incidence over time after implementation of WHO recommended strategies (table 1), these results were not encouraging for the achievement of final goal. There were multiple reasons for this failure. The most important is the inability of surveillance system to capture NT deaths during home deliveries; poor maternal immunization with tetanus toxoid during pregnancy; low socio economic status with poor access to health and delivery services and safe kits, untrained birth attendants with poor cord care and paternal illiteracy. The other important issue is the cultural practices i.e., application of contaminated products on cord, presence of sheep in home premises and gender bias (may be due to early care seeking behavior of parents towards male children and also early circumcision with unsterilized instruments.[5,7,8] The other contributing risk factor for NT is poor knowledge, attitude and practice towards TT immunization during pregnancy especially in population residing in rural area. Nowadays political, law and order situations in Pakistan are an added challenge for elimination of this vaccine preventable disease from our country.

Table 1. WHO/ UNICEF recommended strategies to achieve the MNTE [2]

a. Clean delivery and cord care practices to prevent infection during and after delivery
b. Immunize women during pregnancy with Tetanus Toxoid (TT) or Tetanus Toxoid & Diphtheria (Td) vaccine
c. Immunize women of reproductive age with TT or Td vaccine, through three properly spaced rounds of Supplemental Immunization Activities (TT-SIAs) in high risk areas
d. Reporting of NT to detect and investigate cases and conduct appropriate case response

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This slow speed has led to the extension of duration for MNTE and Government of Pakistan has set it as a target for 2015[4] and adopted high risk approach to achieve the goal. NT has been actively integrated into the acute flaccid paralysis (AFP)/polio surveillance infrastructure in Pakistan with a hope that this integration will improve the reporting efficiency of NT and enhance effective monitoring of TT vaccination coverage.[5] The other step was conducting SIAs for women of reproductive ages. By the end of 2010, at least three rounds of SIAs had been implemented in 54 out of a total of 135 districts, compared to 64 out of a total of 121 districts in Pakistan by the end of 2003. Coverage with the third dose of TT vaccine was 84% during the first phase and 73% during second phase of the SIAs conducted between 2001 and 2003.[6] Also education of untrained birth attendants and dais and provision of clean kit has also helped in decreasing the burden of this fatal disease.

All the mentioned risk factors are leading to low maternal immunity against Tetanus and also more exposure of newborns to this organism ultimately ending up in failure to achieve maternal and neonatal elimination of this fatal disease but with sincere efforts and strengthening of WHO recommended strategies we can make the difference. Enhancing the surveillance is the key. Active surveillance should be more closely followed for NT, in fact general practitioners and pediatricians should be sensitized and provided with resources and easily accessible methods to report NT because without this we cannot identify the high risk behaviors of health care professionals and high risk areas. This would also help in gaps in knowledge and could be easily filled by proper guidance. After the recognition of high risk areas second step should be the SIAs to vaccinate pregnant and women of reproductive age TT. This not only strengthening the EPI but ultimately help in enhanced vaccine coverage which is the ultimate desire in tetanus elimination. But these SIAs and efforts for EPI should be preceded by

education and awareness of people in high risk areas towards this disease and its consequences. This goal can be achieved with the help of lady health workers (LHWs). It is proven that antenatal interventions by LHWs has helped greatly in improving neonatal mortality,[9] so utilizing them will help in winning the battle against NT. They will not only educate the mother for this disease but with their help training of traditional birth attendants can be reinforced. Most of the developing countries have the same challenges to face for MNTE but the political situation in Pakistan is an added issue to be solved. This difficult situation needs wise handling not only by Government of Pakistan but also from international organizations and WHO so that we can achieve our goal for 2015, only a year ahead. It seems difficult but only with aggressive efforts and positive attitude we can do it.

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World Rabies Day 2013

September 28 is celebrated as World Rabies Day (WRD). This year as in previous years there was a huge effort to highlight rabies and bring it to the forefront of public awareness.

Members of IDSP, along with EMRO, RIA Pakistan Chapter, and Society for Neglected Tropical Diseases drove to Hyderabad. Around 100 volunteers, health care workers, nurses and school children had gathered at the Press Club for a rabies awareness program. TV and print press were well represented. We showed startling pictures of bite wounds and a video of patients with rabies; there were speeches and then we announced the opening of a new Rabies Prevention Center to be opened in Civil Hospital Hyderabad

Novartis Vaccines had refurbished the Center at the Civil Hospital with wound washing area and overhead water tank. EMRO provided needle cutters and vaccine, and *Hakimsons* had donated 50 vials of Equine Rabies Immuneglobulin (ERIG). The Director General Health accompanied us to inaugurate the Center.

EMRO/WHO Pakistan has received funds for establishingten Rabies Prevention Centers in Sindh hospitals. Prior to refurbishing these centers, Indus Hospital, Karachi, was officially designated as Rabies Training Center for doctors and paramedics in Sindh. We have conducted training for 30 trainees over four two-day intensive hands-on workshops.

The cities represented are Nawabshah, Mirpurkhas, Badin, Larkana, Jacobabad, Dadu, Sukkur, MirpurMathelo, Hyderabad, Liaquatabad and Civil Hospital, Karachi. Doctors and paramedics from several private hospitals in Karachi also took part. The trainees are now ready to manage dog bites independently in their hometowns instead of sending victims to Karachi for post exposure prophylaxis

Naseem Salahuddin
Head, Department of ID, Indus Hospital, Karahi. President Rabies in Asia, Pakistan Chapter.

Instructions to Authors

Scope

The Infectious Diseases Society of Pakistan sponsors the Infectious Disease Journal of Pakistan (IDJ). The Journal accepts Original Articles, Review Articles, Brief Reports, Case Reports, Short Communications, Letter to the Editor and Notes and News in the fields of microbiology, infectious diseases, public health; with laboratory, clinical, or epidemiological aspects.

Criteria for publication

All articles are peer reviewed by the IDSP panel of reviewers. After that the article is submitted to the Editorial Board. Authors may submit names and contact information of 2 persons who potentially could serve as unbiased and expert reviewers for their manuscript, but IDSP reserves the right of final selection.

Submission of the Manuscript

Manuscripts must be formatted according to submission guidelines given below, which are in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (originally published in N Engl J Med 1997;336:309-15). The complete document appears at www.icmje.org. Please submit one complete copy of the manuscript and all enclosures to **The Managing Editors, Infectious Diseases Journal of Pakistan, Department of Pediatrics & Child Health, The Aga Khan University, Stadium Road, P.O. Box 3500, Karachi 74800, Pakistan.** An electronic copy of the manuscript must also be sent to pak_idj@yahoo.com**.** All manuscripts submitted to IDJP must be accompanied by an Authorship Declaration stating that *'The authors confirm that the manuscript, the title of which is given, is original and has not been submitted elsewhere.Each author acknowledges that he/she has contributed in a substantial way to the work described in the manuscript and its preparation'*. Upon submission a manuscript number will be assigned which should be used for all correspondence.

Manuscript Categories

I. Original Articles

Articles should report original work in the fields of microbiology, infectious disease or public health.The word limit for original articles is 2000.

Title page

This should list the (i) title of the article, (ii) the full names of each author with highest academic degree(s), institutional addresses and email addresses of all authors. (iii) The corresponding author should also be indicated with his/her name, address, telephone, fax number and e-mail address. (iv) A short running title of not more than 40 characters (count letters and spaces) placed at the foot end of the title page.(v) a conflict of interest statement should also be included in this section.

Abstract

Abstract should not exceed 250 words and must be structured in to separate sections headed *Background, Methods, Results and Conclusions*.

Please do not use abbreviations or cite references in the abstract. A short list of four to five key words should be provided to facilitate.

Background

The section must clearly state the background to the research and its aims. Controversies in the field should be mentioned. The key aspects of the literature should be reviewed focusing on why the study was necessary and what additional contribution will it make to the already existing knowledge in that field of study. The section should end with a very brief statement of the aims of the article.

Materials and Methods

Please provide details of subject selection (patients or experimental animals). Details must be sufficient to allow other workers to reproduce the results. The design of study and details of interventions used must be clearly described. Identify precisely all drugs and chemicals used, including generic name(s) and route(s) of administration All research carried out on humans must be in compliance with the *Helsinki Declaration*, and animal studies must follow internationally recognized guidelines. The authors are expected to include a statement to this effect in the Methods section of the manuscript. A description of the sample size calculation and statistical analysis used should be provided.

Results

Present results in logical sequences in the text, tables and illustrations. Articles can have a maximum of 5 illustrations (in a combination of figures and tables) per article. The results should be in past tense and repetition of results presented in the tables should be avoided. Exact *P*-values should be reported along with reporting of OR and RR with their Confidence Intervals where applicable.

Discussion

Emphasize the new and important aspects of the study and conclusions that follow from them. Do not repeat the details from the results section. Discuss the implications of the findings and the strengths and limitations of the study. Link the conclusions with the goals of the study but avoid unqualified statements and conclusion not completely supported by your data.

Acknowledgments

Acknowledge any sources of support, in the form of grants, equipment or technical assistance. The source of funding (if any) for the study should be stated in this section. Please see below for format of **References, Figures and Tables**.

II. Review Articles
Authoritative and state of the art review articles on topical issues are also published, with a word limit of 2000. It should consist of critical overview of existing literature along with reference to new developments in that field. These should be comprehensive and fully referenced. Articles should contain an Abstract; Main Text divided into sections, Conclusions and References.

III. Brief Reports
Short clinical and laboratory observations are included as Brief Reports. The text should contain no more than 1000 words, two illustrations or tables and up to 10 references.

IV. Case Reports
Instructive cases with a message are published as case reports. Routine syndromes or rare entities without unusual or new features are invariably rejected. The text should contain no more than 1000 words, two illustrations or tables and up to 10 references. The authorship should not exceed 3-4 persons.

V. Letter to the Editor
These may relate to material published in the IDJP, topic of interest pertaining to infectious diseases, and/or unusual clinical observations. A letter should not be more than 300 words, one figure and 3-5 references.

VI. News and Views
Informative, breaking news updates in infectious diseases from around the world (approx. 200 words).

VII. Notices
Announcements of conferences, symposia or meetings may be sent for publication at least 12 weeks in advance of the meeting date. Details of programs should not be included.

References
Number references consecutively in the order in which they are first mentioned in the text. Identify references in text, tables and legends by Arabic numerals (in superscript). References cited only in tables or in legends to figures should be numbered in accordance with a sequence established by the first identification of the particular table or illustration. Bibliography should be given in order. Authors, complete title, journal name (Abbr), year, vol, issue, page numbers. According to "Uniform Requirements of Manuscripts submitted to Biomedical Journals", as cited in N Engl J Med 1997; 336:309-15.

Tables and Figures
Data reported either in a table or in a figure should be illustrative of information reported in the text, but should not be redundant with the text. Each table must be presented on a separate sheet of paper and numbered in order of appearance in the text. Table should be numbered consecutively in Arabic numerals. Tables andFigures legends should be self-explanatory with adequate headings and footnotes.Results which can be described as short statements within the text should not be presented as figures or tables.

Illustrations
Illustrations should be numbered, given suitable legends and marked lightly on the back with the author's name and the top edge indicated. Original drawings may be submitted although high quality glossy photographs are preferable. They should be kept separate from the text. If possible, figures should be submitted in electronic format as either a TIFF (tagged image file format) or JPEG format. Minimum resolution for scanned artwork is:

- Black& white line illustration (e.g. graphs): 600 dpi
- Black & white halftone illustrations (e.g. photographs): 300 dpi
- Color illustrations: 400 dpi (note that color images should be split CMYK not RGB)

Plagiarism
Authors should refrain from plagiarism and should double check their work before submitting it for publication. Adequate references should be provided for text from other sources.

Authorship criteria
Those who have contributed sufficiently to the conceptualization, design, collection and analysis of data and writing of the manuscript should be granted authorship. Ideally all authors should be from the same department except for studies that are multi center or multispecialty.

Instructions updated - April 2012.
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