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TIMES
TYPHOID INFECTION MANAGEMENT & ERADICATION SUPPLEMENT

In collaboration with

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ADVANCE EDUCATIONAL INSTITUTE AND RESEARCH CENTRE

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TIMES RESOURCE GROUP

TIMES Magazine volume 2 is a sequence of information from Volume 1 regarding typhoid fever clinical information, diagnosis and an understanding for the epidemiology of the disease. Current issue contains the contemporary information about the human adapted bacterial pathogen of typhoid and the complexity of the disease including main barriers to control. This magazine is scientifically executed to familiarize clinicians, microbiologists and epidemiologists with the shifting trends in enteric fever. The contents also cover the results of the survey endorsing the objective of knowledge, attitude and practices of healthcare providers towards this deadly fever as well as the experts reviews about the previous issue. This magazine is an initiative by Getz Pharma in collaboration with MMIDSP (Medical Microbiology and Infectious Diseases Society of Pakistan) and AEIRC (Advance Educational Institute and Research Centre).

Message From MMIDSP

The morbidity of typhoid fever is highly prevalent in Asia with third highest incidence rate in the southeast region. Pakistan is one of the most affected states in this region. The occurrence of the disease has been linked with the considerable variations associated to the seasonal changes and population. The supply and quality of resources is considered the principal factor impacting the spread of typhoid. The causative agents mainly spread due to poor hygiene, lack of sanitation and poor sewerage systems.

Pakistan is considered underprivileged due to its increasing population and depriving availability of resources that further acts as a key contributor and adds up to the burden of healthcare. The initiative of publishing a structured magazine dedicated to typhoid and its related factors is a remarkable step. We believe that TIMES will prove to be a key facilitator in spreading awareness and essential knowledge to all the recipients. MMIDSP recognizes the participation of Getz Pharma in the generation of this magazine as a fruitful approach that will certainly benefit both the professionals and the population of Pakistan.

Prof. Brig. Dr. Aamer Ikram, SI(M)
President MMIDSP

Typhoid Fever: Good Knowledge Leads to Appropriate Actions

A Cross-sectional survey was conducted through TIMES Magazine Volume - 1 during May - July 2017 among Health Care Providers in all four provinces of Pakistan i.e Sindh, Punjab, Balochistan & KPK. The main focus of the survey was to collect information related to Typhoid Fever & the practices of physicians which they follow in clinical examination, diagnosis and treatment of Typhoid Fever. The survey was conducted to understand public health risks related to Typhoid Fever and how the practicing physicians are dealing with patients in their routine clinical practices.

The survey consisted of eight questions. Three questions were about clinical examination and confirmation test, while two questions were focused towards contributing factors and reasons of relapse for Typhoid. However, remaining questions gathered information on prescribing practices, factors for resistance and drug of choice among health care professionals. All the questions were closed ended and responses were recorded on pre designed questionnaires.

The survey was distributed to 1800 participants, and responses were received from (n=1135) for which results are shown below. Most of the respondents were general practitioners who treat Typhoid patients in their routine clinical practice.

Demographics

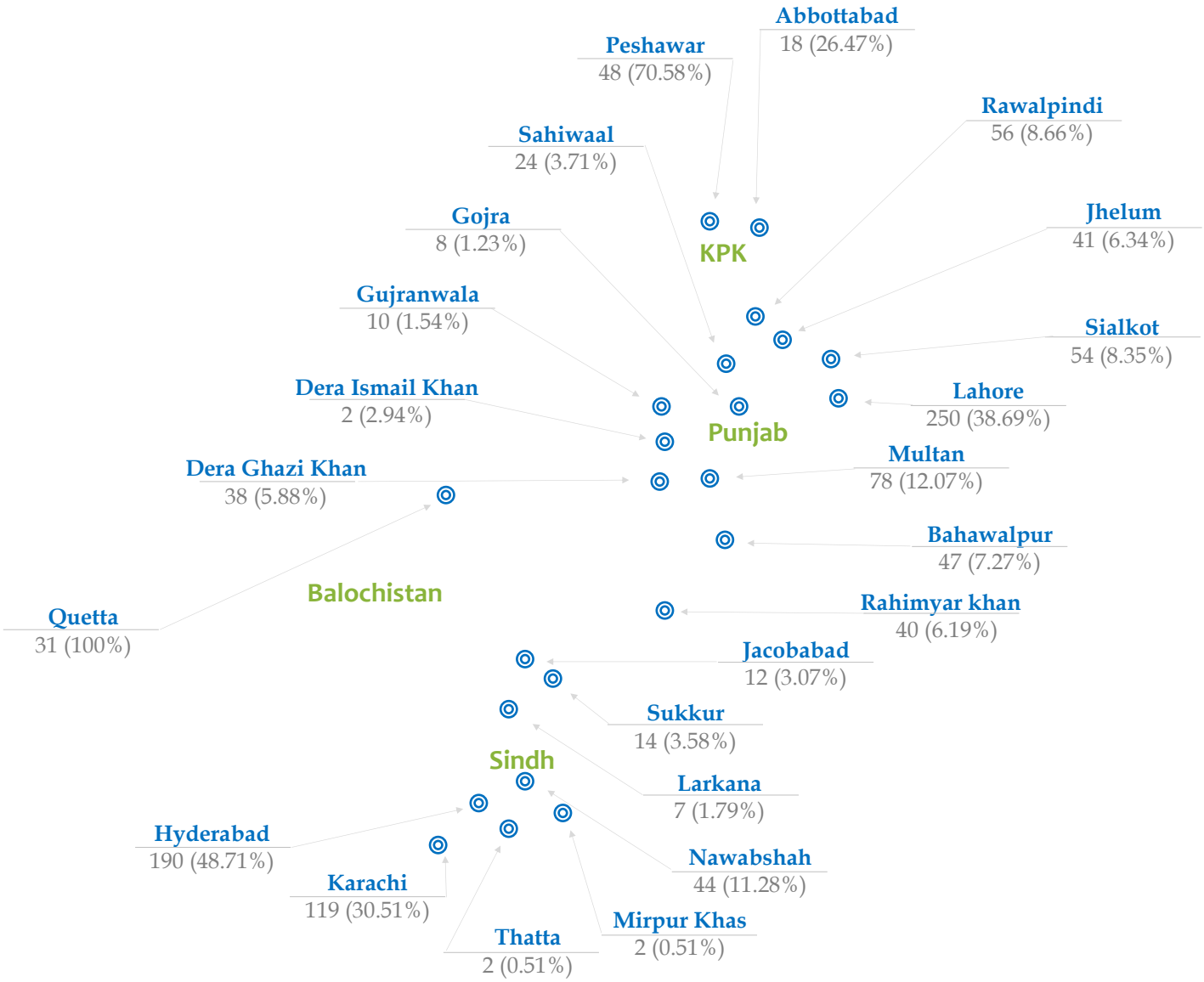
The number of responses received from each province are tabulated below.

Table 1: Number of responses from four provinces of Pakistan

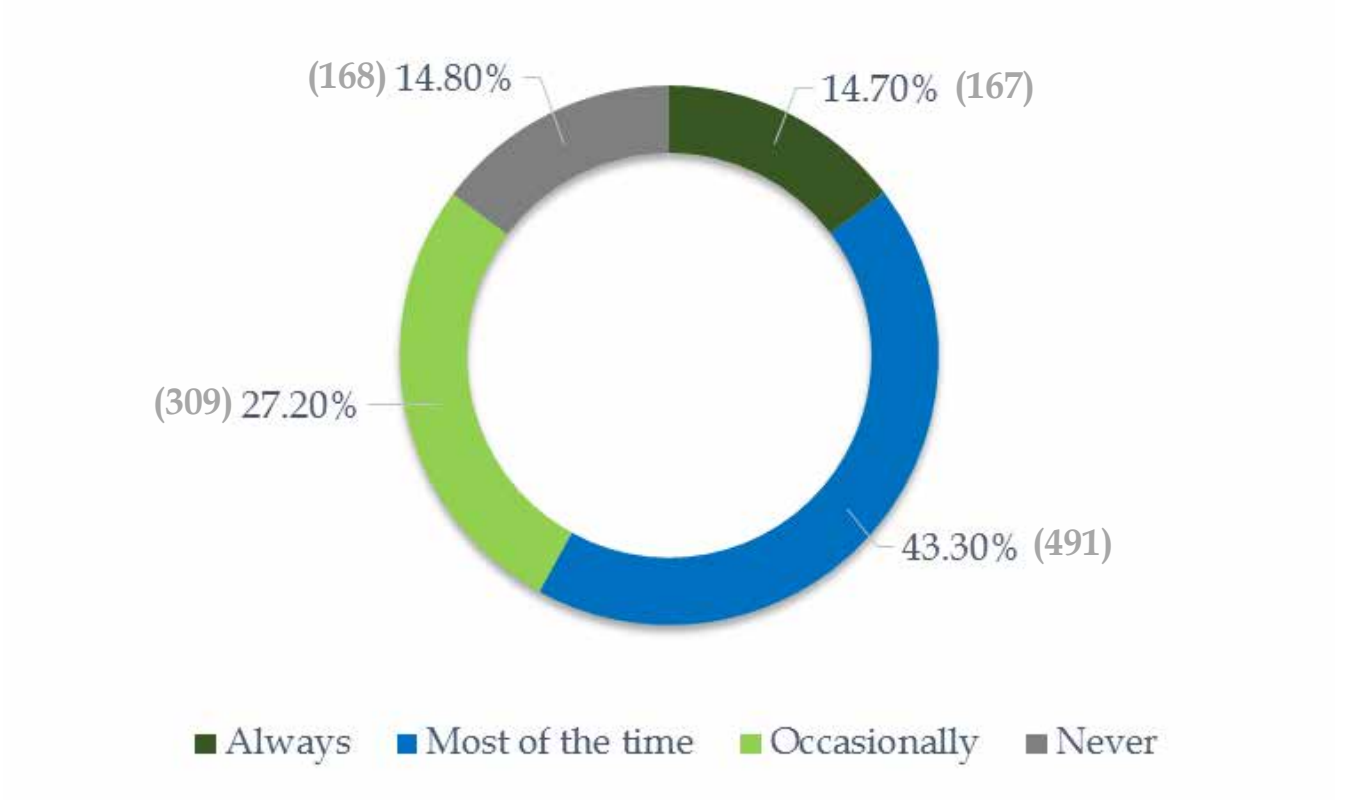
Province	n (%)
Punjab	646 (56.9%)
Sindh	390 (34.4%)
KPK	68 (6.0%)
Balochistan	31 (2.7%)

The survey was disseminated in all major cities throughout Pakistan. The city wise distribution shows that the maximum number of responses were received from Lahore (n=250) which is the provincial capital with a high number of health care providers. Though Baluchistan is the largest province as per area distribution but we could only cover Quetta and received responses from (n=31) physicians. The two largest participating cities from Sindh were Hyderabad (n=190) and Karachi (n=119).

City Wise Distribution of Responses From Each Province of Pakistan



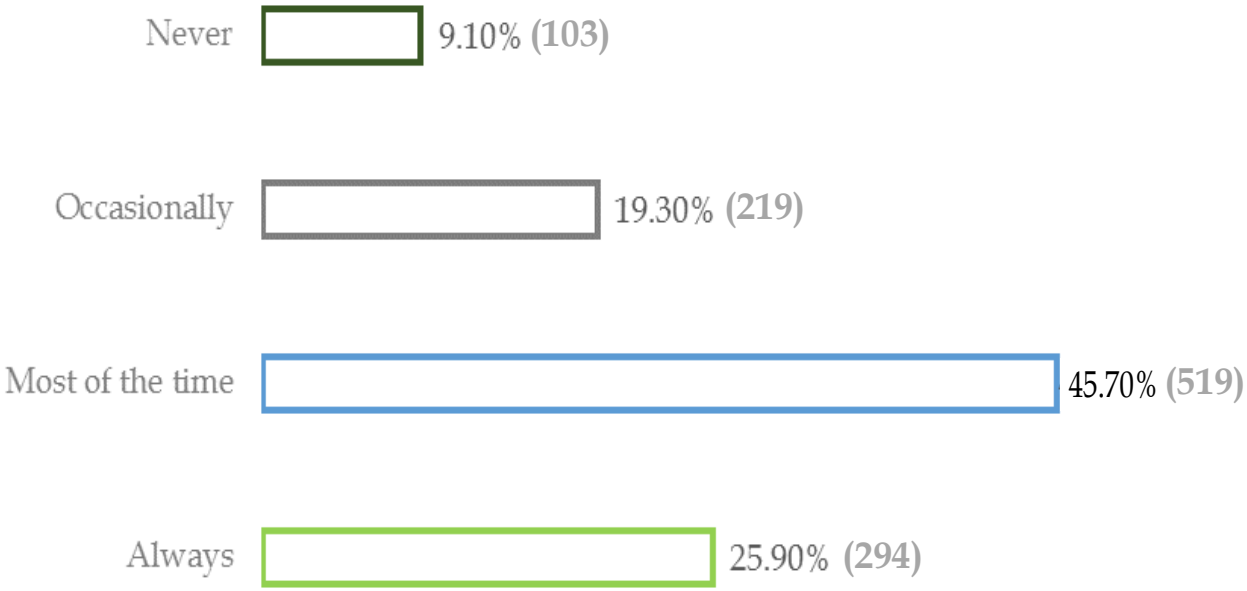
Diagnosis of Typhoid Fever through Clinical Examination



Graph 1: Showing frequency of opting clinical examination for Diagnosis of Typhoid Fever by health care providers

The results showed that 43.3% Health Care Providers diagnose Typhoid Fever through clinical examination, most of the time. The data shows that there was a high percentage of physicians from Baluchistan who diagnose typhoid on clinical basis, followed by Sindh and Punjab. However KPK has the highest number of physicians who diagnose occasionally on clinical basis. As reported in the previous studies most of the clinically diagnosed typhoid cases were misdiagnosed and the hue and cry by the general public on the epidemic of typhoid fever could not be justified. It is recommended that cautious and detailed history taking, meticulous clinical investigation and prompt bacteriological culturing of specimens from suspected typhoid cases will improve the accuracy of clinically diagnosed typhoid fever (1).

Prescribing Empirical Antibiotic for Typhoid Fever



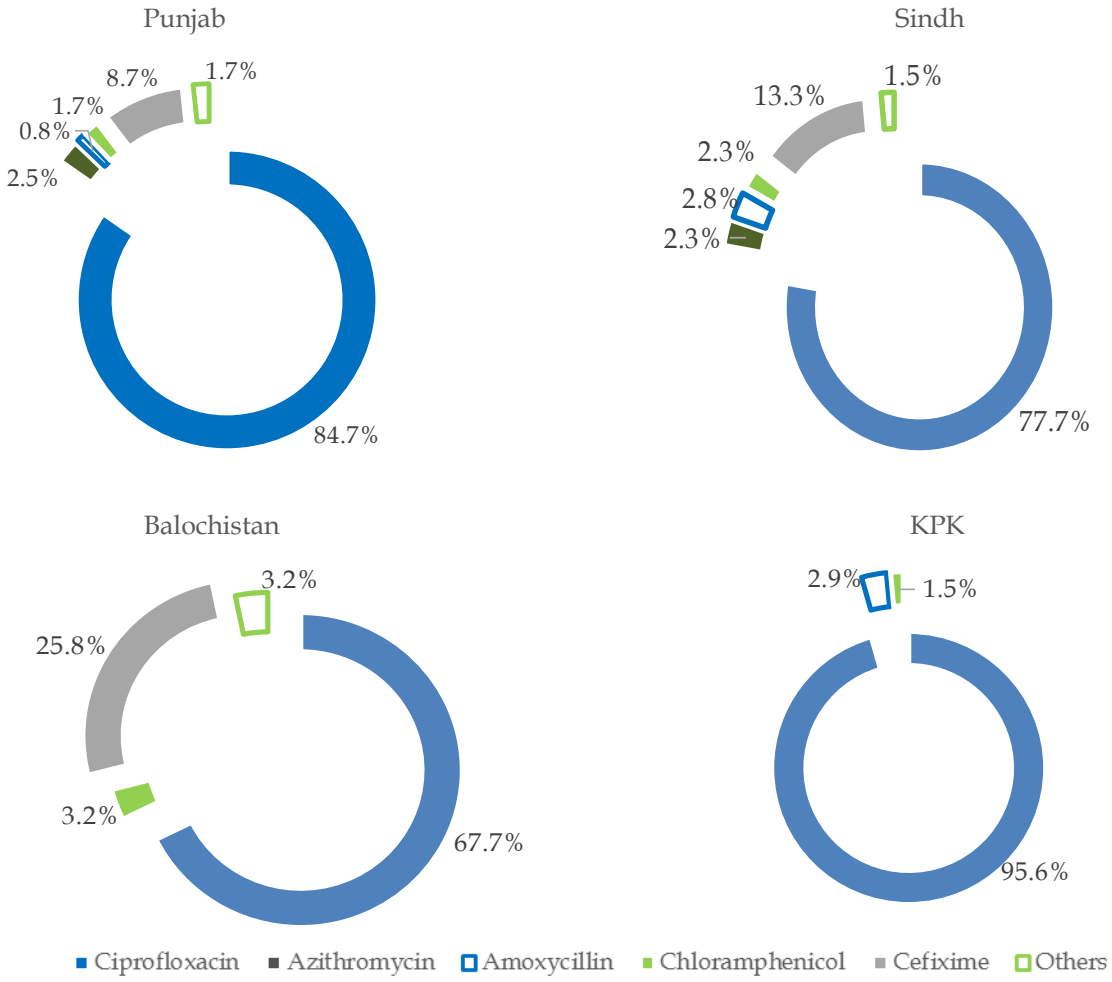
Graph 2: Showing frequency of prescribing empirical antibiotic for Typhoid Fever by health care providers

The results indicate that 45.7% health care providers prescribe empirical antibiotic for Typhoid Fever, most of the time. The data shows that KPK has the lowest percentage of physicians who prescribe empirical antibiotic for typhoid fever. Daniel R. Diniz-Santos and his colleagues in a study suggested once Ampicillin and trimethoprim-sulfamethoxazole (TMP-SMX) were considered as drugs of choice for the empirical treatment of outpatients with acute infection caused by typhoid that usually occur because of *Shigella or Salmonella* because of their efficacy, safety and affordability. With the passage of time, outbreaks of such infections caused by *Shigella or Salmonella* strains became resistant to one or both of them (2). Even though these antibiotics may still be useful against some bacteria infecting outpatients or inpatients in various parts of the world, the resistance of many pathogens against the antibiotics has reached such high rates that their extensive empirical use can no longer be suggested (3). The empirical choice of the antimicrobial agent must be made individually for each case, considering the safety, affordability and efficacy of the drugs, the pathogens most likely to be infecting the patient and up-to-date knowledge of the vulnerability pattern of locally circulating strain (4).

Antibiotic Prescribed to a Suspected Typhoid Fever Patient

	n	%
Ciprofloxacin	936	82.5
Azithromycin	25	2.2
Amoxycillin	18	1.6
Chloramphenicol	22	1.9
Cefixime	116	10.2
Others	18	1.6

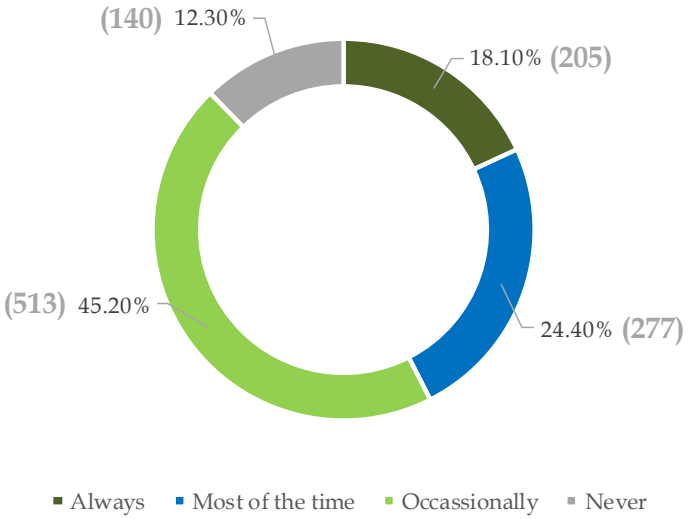
Table 2: Showing n (%) of antibiotic prescribed to a suspected typhoid fever patient



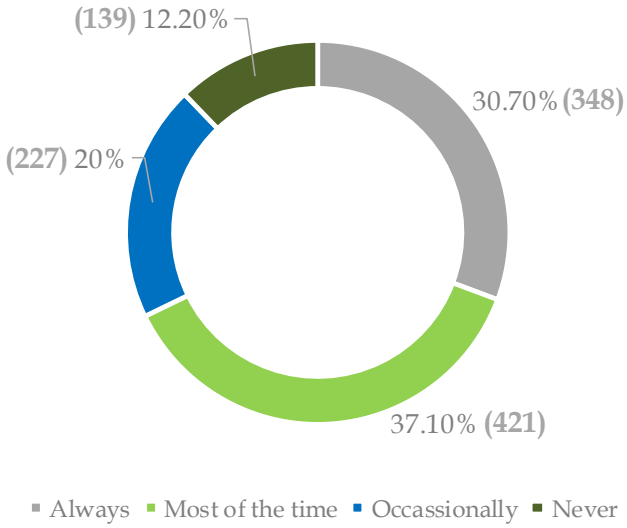
Graph 3: Showing frequency of Antibiotic prescribed to a suspected typhoid fever patient in province of Punjab, Sindh, Balochistan & KPK

The data indicates that Ciprofloxacin is the most common drug of choice usually prescribed by most of the doctors empirically in suspected typhoid fever patients. As stated by Center for Disease Control and Prevention (CDC), Azithromycin and Ceftriaxone are used to treat typhoid fever or paratyphoid fever because of the emergence of multidrug-resistant strains, although an increasing resistance to Azithromycin in *Typhi* strains has been recognized. In contrast, no cases of ceftriaxone resistance have been reported among *Typhi* and *Paratyphi A*. isolates tested by the CDC National Anti-microbial Monitoring System (2-5).

Refer Patients for Blood Culture



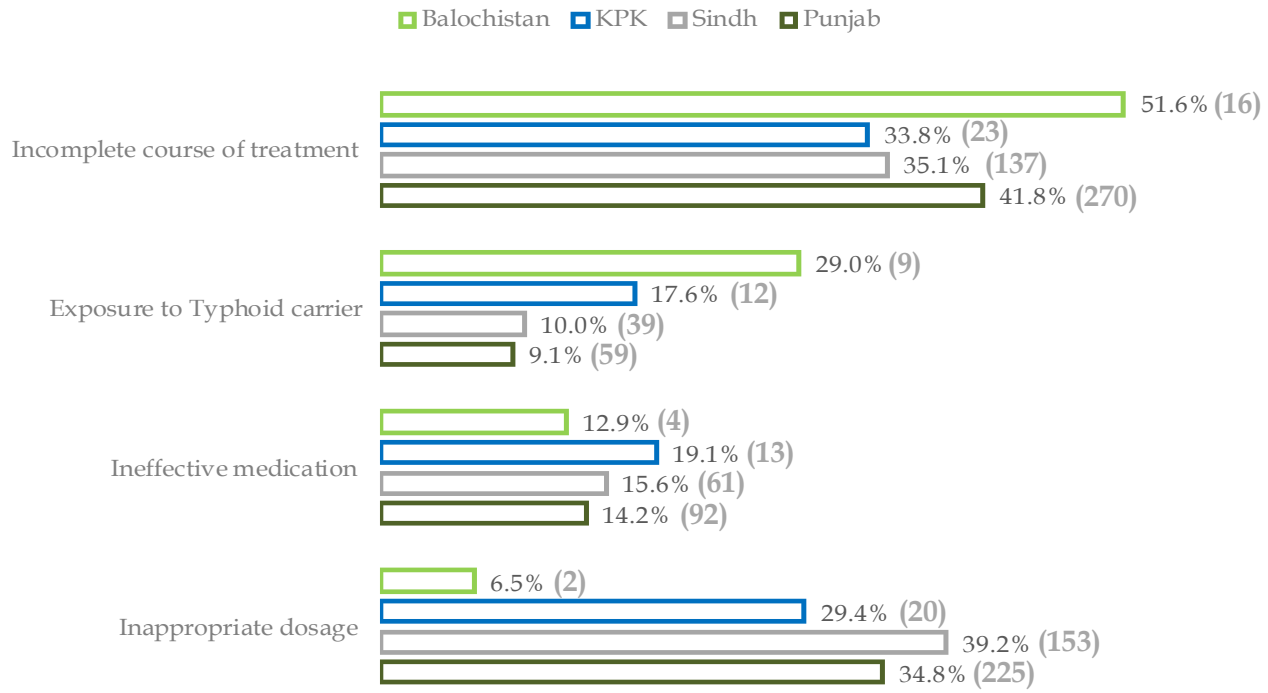
Graph 4: Showing frequency of referring patients for blood culture by health care providers in all four provinces.



Graph 5: Showing frequency of preference for newer diagnostic test i.e., Typhidot test

Graph 4 indicates that 45.2% Health Care Providers refer patients for blood culture occasionally while 20% health care providers always prefer for newer diagnostic test i.e., Typhidot Test and 37.1% consider it most of the time (Graph 5) However, Globally Typhidot test did not provide as favorable results as clinicians expect it to. It showed very low sensitivity and specificity despite being speedy and easy to perform. According to the information provided in CDC, Blood culture is the mainstay of diagnosis in typhoid and paratyphoid fever (6). The diagnostic criteria increases in 80% of the cases with bone marrow culture and is comparatively unaffected by previous or parallel antibiotic use. However, stool culture is not usually so efficient for diagnostic purposes during the first week of illness, because there is no definitive serologic test for typhoid or paratyphoid fever, early diagnosis often has to be made clinically (7).

Major Factors of Relapse



Graph 6: Showing number of responses for major factors of relapse from four provinces of Pakistan

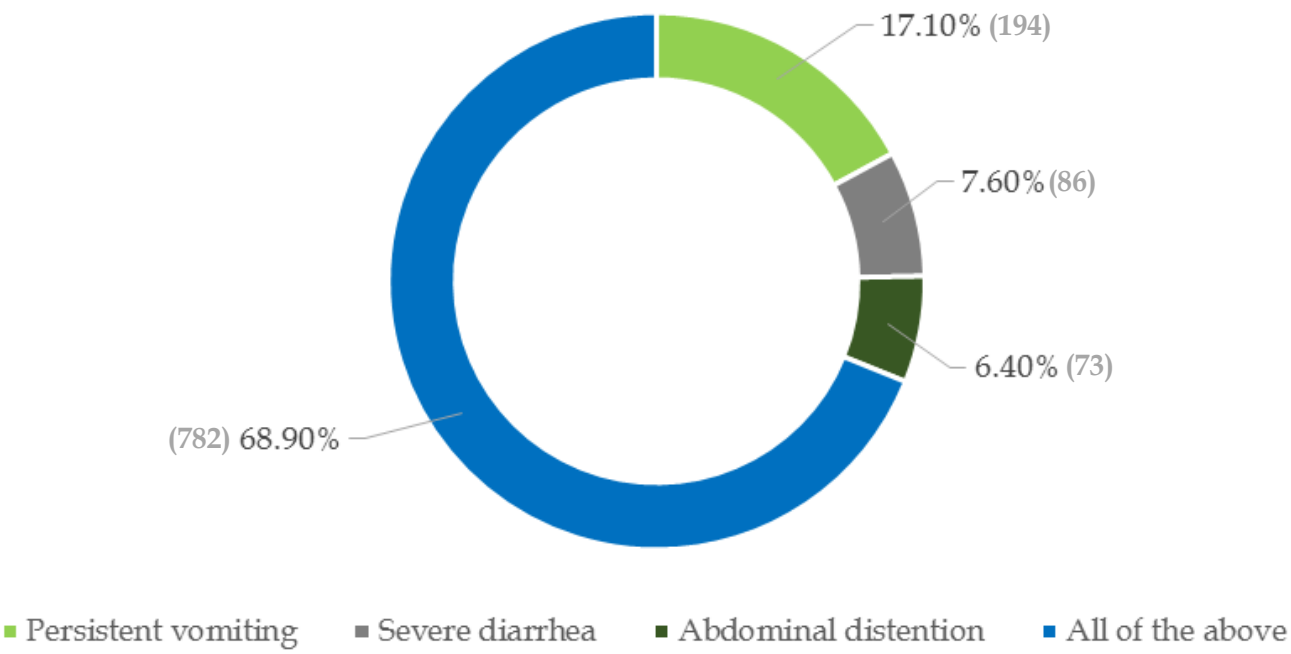
The graph represents that the inappropriate dosage & incomplete course of treatment remains the major factors of the relapse of typhoid. According to the study published in "The Journal of Infection in Developing Countries", the major factors that cause typhoid relapse are (8):

1. Ineffective Treatment
Stronger antibiotic treatment is required for treating patients who usually fail to complete the previous antibiotic course that may develop antibiotic. It must be ensured that the patient is completely taking all the doses of antibiotics as prescribed for the treatment of typhoid even if they begin to feel better within a few days after taking medication.

2. Vaccine Ineffectiveness
Vaccine ineffectiveness is another major cause of relapse. Typhoid vaccines are not 100 percent operative and patients who fail to observe other preventative procedures may become re-infected with typhoid fever. Typhoid vaccines become ineffective after several years and people at risk require promoters every two years for inactivated vaccines and every 5 years for live oral typhoid vaccines.

3. Typhoid Carrier
According to CDC, patients who recently recover from typhoid may still carry the bacteria in their bloodstream and other body organs. Such people are called typhoid carriers and they continue to shed this infecting bacteria in their feces and urine. Typhoid carriers are more likely to have a typhoid fever relapse because the bacteria that causes typhoid is already present in their bodies.

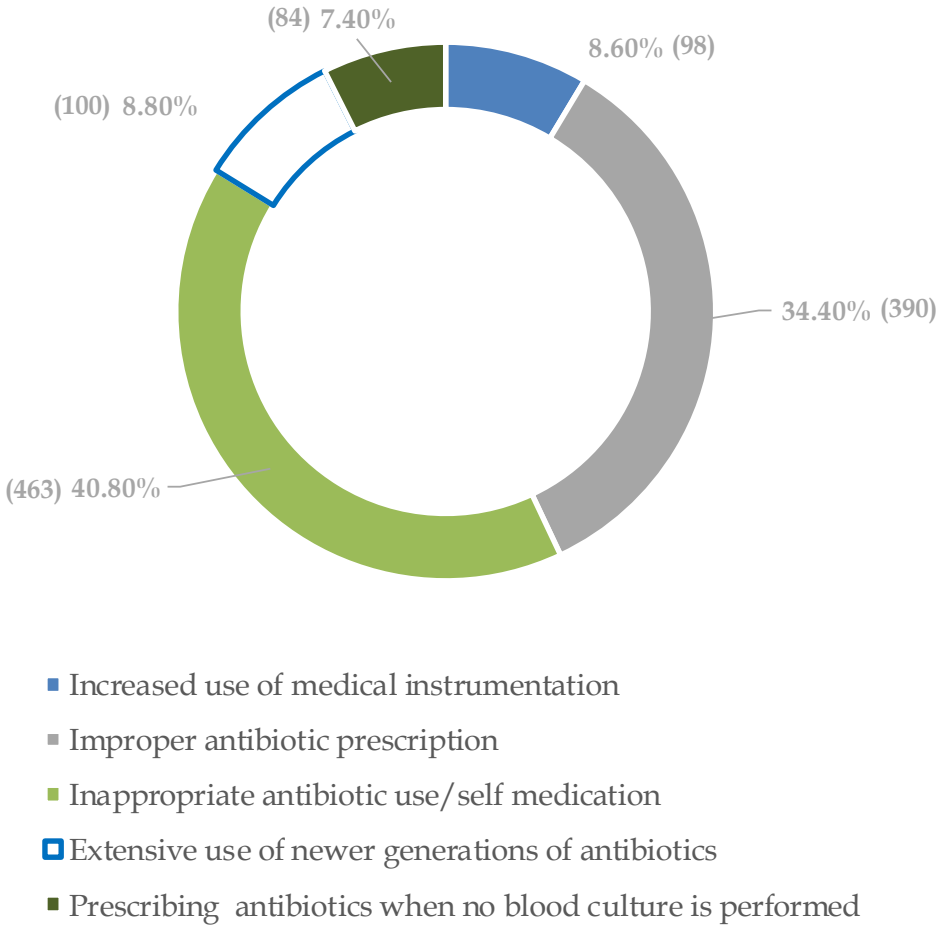
Prescribing Parenteral Antibiotic in Typhoid Fever



Graph 7: Showing most common indications for prescribing parenteral antibiotic in Typhoid Fever

The graph indicates that all three indications i.e. persistent vomiting, abdominal distention & severe diarrhea are the common reasons to prescribe antibiotic in typhoid fever. Diarrhea characterized by liquid stool containing large quantities of leukocytes and protein along with consistent vomiting is resolved by treatment with Chloramphenicol. Among all antibiotics used to treat typhoid Chloramphenicol is found to be the most effective drug for treatment of the acute illness, if the organism is not resistant. Ampicillin and Amoxicillin are also effective alternatives. Mortality rate is less than 1 percent with antibiotic treatment (9).

Major Factors of Bacterial Resistance



Graph 8: Showing comparison of responses about major factors of bacterial resistance

The graph represents that (n=463) 40.8% bacterial resistance are due to inappropriate antibiotic use/self medication while the second most reported factor (n=390) 34.4% was improper antibiotic prescription. According to the report of Centers for Disease Control and Prevention (6), main causes of bacterial resistance to antibiotics have been linked to over-prescription of an antibiotic, incomplete antibiotic course, overuse of antibiotics, Poor infection, hygiene control in health care settings and absence of new antibiotic discovery. Minimizing resistance should therefore be considered comprehensively by resistance mechanism, microorganism and antimicrobial drug (10-12).

Commentary

CARRIER CASES OF TYPHOID FEVER

Dr. Yousuf Kamal Mirza

Dr. Yousuf Kamal Mirza is a consultant at AKUH and Medilink Hospital. His research and therapeutic interests include Infectious Diseases and Public Health.

Typhoid fever can be transmitted from person to person or by ingestion of food or water contamination either by urine or feces of acute cases or carriers. Common symptoms include insidious onset of persistent fever, headache, malaise, anorexia, constipation (more commonly than diarrhea), bradycardia, splenomegaly, and rose spots on the trunk.

Approximately 10% will shed bacteria among the untreated acute cases, for three months after the initial onset of symptoms and 2% to 5% are suspected to become chronic typhoid carriers (13).

Types of Carriers

Convalescent Carriers

A person who carries typhoid bacilli for three or more months after onset is a convalescent carrier. Convalescent carriers may be released when three consecutive negative specimens of feces and urine taken at intervals of not less than one month, beginning at least one week after discontinuation of specific therapy are obtained. Such a release may be granted at any time from 3-12 months after onset. Convalescent cases can be a serious problem with many forms of diarrheal diseases, like shigella and sonne dysentery. It can remain infectious for long periods, especially when typhoid bacilli invades in such organs like gall bladder (14).

Chronic Carriers

If a person excretion of typhoid bacilli continues for more than 12 months after onset of typhoid fever, he/she is considered as a chronic carrier. Any individual who have no previous history of typhoid fever or who had the disease more than one year previously, and whose feces or urine are found to contain typhoid bacilli on two separate examinations at least 48 hours apart, is also defined as a chronic carrier. A chronic carrier state (excretion for more than one year) occurs approximately in almost 5% of the cases. Chronic carriers are considered asymptomatic by definition (15).

Chronic fecal carrier continue to pass bacilli intermittently in the excreta at least one year after infection.
Chronic urinary carrier the renal pelvis is infected and the bacilli pass in urine.

Cases and Carriers

Both may possess an increased risk of spreading infection i.e. food handlers, staff of healthcare facilities, children less than 5 years of age, older children or adults who cannot maintain good standards of personal hygiene pose a greater risk of spreading typhoid. Both cases and carriers of *S. typhi* should be ultra-careful in their hygiene practices. Carriers should be referred for specialist clinical management (16).

Risk of Typhoid Carriers

Typhoid fever represents a greater risk for pediatric and adult travelers from industrialized countries who visit the developing countries (17). In public areas, chronic gall bladder carriers usually adult females who excrete large amount of typhoid bacilli constitute a key reservoir of infection (18). In areas with low hygiene, fecal contamination from in apparent carriers (chronic or temporary) and clinically ill patients can

contaminate water supplies. If there is inadequate or unavailable treatment of water sources, this contaminated water can serve as an important vehicle of transmission (17 & 18). Depending on the age of the infected patient, the pre-existing gall bladder pathologies, and the specific antibiotic treatment administered, up to a few percent of infected persons are susceptible to become chronic gall bladder carriers, thereby maintaining the reservoir of infection. However, a fairly long incubation period upto about 8–14 days follows the ingestion of typhoid bacilli before the onset of clinical disease. Hence there is a vital need to increase the chance of detecting the carriers so as to decrease the risk of spreading typhoid to the communities. In urban areas where the sewage clearance is lacking or inadequate, contaminated water supplies and due to such conditions typhoid fever is common among these areas. The contamination of food by food handlers who are mainly carriers, forms the second commonest route of infection. Since spread of the disease is via fecal-oral route, so attempts at breaking the transmission cycle would play an important role in the effective control of the disease (17).

The typical general features of typhoid include fever (that increases in step-wise fashion and persists for weeks if treated improperly), moreover headache, and abdominal discomfort is commonly observed. In 1937, a man employed to lay water pipes in Croyden, England, was found to be the source of a severe epidemic of Typhoid Fever.
The man, asymptomatic carrier of salmonella enterica serotype typhi, habitually urinated at his job site. In the process, he contaminated the town's water supply with bacteria from his bladder. Over 300 cases of typhoid fever developed, and 43 people died before the man was identifies as carrier.

Marry Mallon-Typhoid Carrier
Mallon was suspected to have infected 51 people, out of which three died. Since she used a number of pseudonyms, it's possible that the real death toll could have been higher. However, based on the confirmed mortalities, Typhoid Mary was not even the most fatal carrier of the typhoid germ in New York City's history. In 1922, New Yorker Tony Labella reportedly caused two outbreaks that combined for more than about 100 cases and out of which five died. Although she harbored the extremely transmittable bacteria that cause typhoid fever and never revealed any of the obvious symptoms. Mallon herself was immune to the disease, she was the first person in the United States identified as an asymptomatic carrier of the pathogen.

Doctors hypothesized that Mallon likely passed along typhoid germs by failing to vigorously scrub her hands before handling food. However, since the elevated temperature that is necessary to cook food would have killed the bacteria, however Soper wondered just how Mallon could have transmitted the germs. The answer of his question was in one of Mallon's most popular dessert dishes—ice cream with raw peaches cut up and frozen in it (18).

Control of Typhoid Outbreaks Include
There must be an increased screening of food as well as water samples to trace the source of the etiological agent. Availability of diagnostic tests that are rapid, sensitive, specific, easy to perform and also cost effective to detect for the pathogen in contaminated food, water and healthy human carriers, would provide be an effective tool in controlling and preventing typhoid.

The present gold standard to detect for carriers is by means of stool culture. This is not only tiresome and expensive but also has a low sensitivity (19). Multiple bacteriological examination of stools are also essential to make a reliable diagnosis due to intermittent or light fecal excretes among carriers. There have been studies on carriers that showed positive fecal culture only after 196 negative culture results (20). Recent studies have shown that there is an increased risk of gallbladder carcinoma among typhoid carriers (19-22). Hence, a test to detect for typhoid carriers that is cheap, sensitive, specific would promote not only effective management of the disease but also reduce gallbladder carcinoma and dysfunction.

Commentary

RELAPSE OF TYPHOID FEVER

Dr. Mujeeb-ur-Rehman Abid Butt

Professor Dr. Mujeeb-ur-Rehman Abid Butt is a consultant at the Shalamar Hospital/ Shalamar Institute of Health Sciences. His research and therapeutic interests include Infectious Diseases and Enteric Fevers.

Typhoid fever or simply Typhoid is caused by *Salmonella enterica* serotype *Typhi*. It is a food and water born infection. Peak incidence worldwide is during hot and humid months of a year. In Pakistan, maximum cases are seen during the monsoon seasons and few weeks subsequent to it. Incidence in Pakistan and the neighboring south eastern countries is more than 100 cases/100,000 per year and in Bangladesh this rise up to 2000 cases/100,000 during peak season (23). Typhoid is one of the most commonly encountered febrile illness in the developing countries including Pakistan. Patient generally presents with fever, headache, abdominal discomfort, cough, lethargy and myalgias. There are many complications associated with typhoid presenting in variable proportions depending upon the individual's premorbid state and the virulence of the *Salmonella*. These include myocarditis, encephalopathy, neuritis, meningitis, pneumonia, disseminated intravascular coagulation, hemolytic anemia, focal abscess formation and relapse (24).

Relapse occurs in 5-10% of the cases and is the recurrence of clinical features consistent with typhoid proven by positive blood culture manifesting within 2 weeks of successful completion of antibiotic course for the preceding episode of typhoid (25). Studies have shown that relapse can occur from day 1 to day 70 from the day of stopping antibiotics. Mechanisms of acquiring the bacterium that is *Salmonella typhi*, in the relapse phase includes either recrudescence or reinfection.

In recrudescence, there is regrowth of *salmonella* from the sites where it had remained in dormant phase during asymptomatic phase after the previous course of antibiotics. In order to prove recrudescence the molecular typing is done from the culture plates and it has to be the same as it was in the preceding episode (26). The sensitivity to antibiotics will be the same as it was in the preceding episode in such relapses which signifies that the same strain of salmonella causes the relapse. This point highlights the significance of doing blood cultures in patients suspected or suffering from typhoid fever. In reinfection, the salmonella gets the opportunity to get into the human body again through its usual mode of transmission and it can either be the same strain which infected the patient earlier or it may be the different strain (27).

As *Salmonella typhi* infection does not confer long term immunity, so the individual remains prone to get reinfection by the same strain of salmonella or by other strains. Either it is recrudescence or reinfection, it has been observed that patients with relapse are less toxic and the magnitude of fever is low (25 & 28). Response to antibiotics have also been seen very effective during the relapse phase so much so that the defervescence time, that means the time duration of fever regression from the start of antibiotics, also gets shortened during relapse.

Reasons for the milder course of disease in relapse includes better dealing of the patient as one can expect for any case coming again for the consultation for recurrence of fever and prompt initiation of therapy provided there is a high index of suspicion on behalf of treating doctor (29). It has also been suggested that the reduced immune generation during any episode of typhoid fever reflected in the shape of negative typhidot IgM test is probably one mechanism through which *Salmonella* escapes the immune clearance and result in the relapse of infection (30).

It has also been observed that irrespective of being the milder nature of disease during the relapse phase of typhoid, patients tend to stay longer as compared to the cases admitted for their first episode of typhoid. Reasons again require more vigilance on behalf of the treating physician as well as the prolonged course of antibiotics.

Studies have shown that relapse are considerably less with the use of Ceftriaxone and Quinolones for the first episode of typhoid. Though, there had been controversy in choosing antibiotics for the acute phase of typhoid but a report in 1992 showed that 7 days therapy with Ciprofloxacin is considered to be the best drug to treat typhoid and average defervescence time ranges between 3 to 21 days with no relapse. Later trials by Rupali et al (31) found that treatment failure with ciprofloxacin was found in 17.4% cases with a mean defervescence time of 12.4 days.

Individuals with relapse respond very well to the same antibiotics to which he/she responded on the first occasion. Identification of the organism during relapse phase becomes easier if the sensitivity pattern is same during the relapse as that of the preceding episode of typhoid but molecular genotyping such as Pulse Field Gel Electrophoresis is the only way to confirm the actual relapse with the same previous *Salmonella* (27).

Trials performed in Pakistan (32) in 2000 found that the 2 weeks course of ceftriaxone remarkably reduce the chances of relapse. Earlier in Egypt it was found that 5 days course of ceftriaxone causes 95% cure rate and marked reduction of relapse (33).

Antimicrobial treatment of typhoid fever has evolved in the last over 70 years after the invention of chloramphenicol and after the discovery of multidrug resistance with *Salmonella* in late 1970s, there has been diversity in the treatment of typhoid among different geographical groups. It has now become an absolute necessity that the local sensitivity pattern of *Salmonella typhi* may be checked and published sequentially so as to make a protocol for treating typhoid in a said location (25). This is especially true in our part of the world where typhoid is one of most prevalent febrile illness with emerging antibiotic resistance and poor health care facilities.

Commentary

REASONS OF DEVELOPING RESISTANCE AGAINST TYPHOID

Dr. Shahana Urooj Kazmi

Professor Dr. Shahana Urooj Kazmi is Vice Chancellor at Dadabhoy Institute of Higher Education. Her research interests include Clinical Microbiology and Immunology Infectious.

Bacterial infectious disease like typhoid fever is commonly caused by a bacillus *Salmonella typhi*, while other major pathological strains causing paratyphoid fever include A, B and C. *Salmonella* has been recognized as a cause of intestinal diseases for many years. Control of *Salmonella* infection is difficult due to the bacterium's high tolerance to environmental stress, widespread distribution, multiple drug resistance, and adaptability.

Typhoid fever is still one of the most prevalent infectious diseases found during summer season and is considered as one of the most important causes for fever detection in developing countries. Usage of contaminated drinking water and food supplies with faecal wastes may be the basic source for the transmission in areas where it is highly prevalent. In humans, the most common diseases caused by *Salmonella typhi* (a non-capsulated, non-spore forming bacillus bacterium) include gastroenteritis, bacteraemia and enteric fever. With more than 80% of global cases, South Asia is the most commonly reported region for the acquisition of typhoid fever since 1996 to 2005. There are several hospital based studies carried out in Pakistan that describe high incidence rate of typhoid fever in children.

However, hospital based data does not reflect the actual disease status in normal community. Especially in remote areas where people live under low socioeconomic conditions and without basic necessities of life such as water, food, electricity and transport, incidence rate is much higher and often associated with small disease outbreaks. Consumption of unsafe drinking water and inadequate sanitary conditions also contribute in increased rate of typhoid fever.

In remote places, people usually rely on private and unsafe drinking water reservoirs for example ground wells are frequently found in these localities and act as only reservoir of drinking water without proper quality check (34). According to an estimate in 2003, water borne infections claim 250,000 deaths each year in Pakistan among which typhoid fever is the leading cause. In addition with high frequency and easy transmission, typhoid fever outbreaks also accompany with the threat of multidrug resistance.

Multidrug-resistant (MDR) strains of *Salmonella*; resistant to chloramphenicol, ampicillin and trimethoprim are commonly observed since two decades and responsible for numerous outbreaks. A Danish study found that although persons with susceptible *Salmonella* infections had a higher mortality than the general population where as persons with resistant *Salmonella* infections had an even higher mortality. The death rate for persons with multidrug-resistant infections was estimated to be 10 times higher in the two years following specimen collection than for the general population (35).

- One leading factor is the over-prescription by physicians particularly antibiotics, even in the absence of appropriate indications. Such inappropriate practices are often fostered by diagnostic uncertainty, lack of opportunity for patient follow-up, lack of knowledge regarding optimal therapies, and patient demand. In many developing countries, problems typically arise because antimicrobial agents are readily available and can be purchased as a commodity without the advice or prescription of a physician or other trained health care provider.

- Some common types of human behavior also play a role in promoting resistance of particular importance, for example, patient self-medication and noncompliance with recommended treatments. Noncompliance occurs when individuals forget to take medication, prematurely discontinue the medication as they begin to feel better, or cannot afford a full course of therapy.

- Various practices common in hospitals contribute to the resistance problem as well. Indeed, hospitals are especially fertile grounds for breeding resistant microbes.

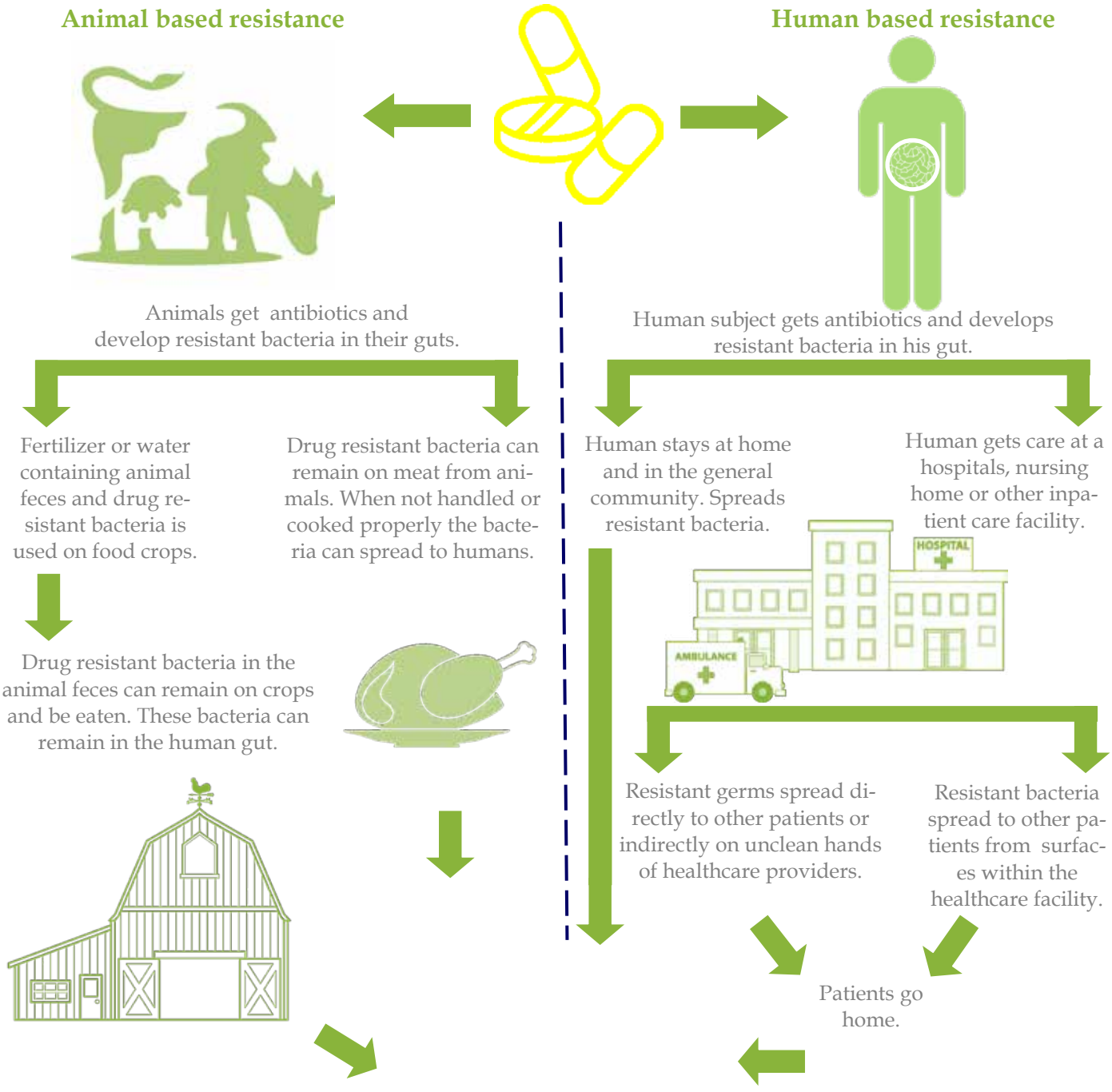
The emergence of *Salmonella* strains that are resistant to commonly used antimicrobials should be particularly noted by clinicians, microbiologists and those responsible for the control of communicable diseases, as well as the food producers including the food industry. Control of drug-resistant *Salmonella* is most efficiently achieved through the reduction of antimicrobial use. Prudent usage in food animals should be combined with good husbandry, good abattoir practice and good hygiene at all stages in the food production chain, from processing plants to kitchens and food service establishments (36 & 37).

These combined efforts should reduce the numbers of the relevant strains in food animals and lower the risk of contamination by resistant *Salmonella* at all stages in the food production chain. It is concluded that typhoid fever is still a burden on developing countries like Pakistan, which is mostly contributed by the rural areas due to improper sanitation and non-availability of the advanced diagnostic facilities for early diagnosis. Thus, it is necessary to build the epidemiological diseases control system as well as antibiotic therapy units in the rural areas in developing countries to control the infectious diseases. It is crucial to ensure safe water supply for drinking and identification of chronic carriers of the bacteria (38).

These combined efforts should reduce the numbers of the relevant strains in food animals and lower the risk of contamination by resistant *Salmonella* at all stages in the food production chain. It is concluded that typhoid fever is still a burden on developing countries like Pakistan, which is mostly contributed by the rural areas due to improper sanitation and non-availability of the advanced diagnostic facilities for early diagnosis. Thus, it is necessary to build the epidemiological diseases control system as well as antibiotic therapy units in the rural areas in developing countries to control the infectious diseases. It is crucial to ensure safe water supply for drinking and identification of chronic carriers of the bacteria (38).

Antibiotic Resistance Spread

(Adopted from World Health Organization, 2014)



Words of Appreciation

"Nowadays, academic activities are not to such an extent. I am glad to appreciate your efforts in this regard. It was very supportive act by the magazine that facilitated the doctors to have recent updates in the diagnosis and treatment of the typhoid fever and above all, local trials are true reflection of our society and provide us with a true picture of the disease in our country."

Dr. M.Yasir Yaqoob
M.B.B.S., F.C.P.S. (Medicine)
Consultant Physician, Assistant Professor of Medicine
Allied Hospital and Punjab Medical College
Faisalabad.

"Typhoid infection management and eradication supplement offered by Getz is an excellent source of information for practicing doctors. I would suggest you to keep updating the previous issues so that it adds on knowledge and information regarding Typhoid."

Dr. Adil Mehmood Ranjha
M.C.P.S., F.C.P.S.
Consultant Physician Medicine
Bahawal Victoria Hospital
Bahawalpur.

"It provides Public awareness on preventive measures against typhoid and induce behavioral changes. This initiative of Getz Pharma in collaboration with SINA Health Education and Welfare Trust is a remarkable and highly appreciable step. This is beneficial in spreading the awareness and essential knowledge to health professional and people of Pakistan and will also help in reducing the health burden."

Dr. Mehmood Ashraf
Consultant Medical Specialist
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A Survey on Follow-up Pattern of Typhoid Patients

1. Do you think a Typhoid patient should be followed after completion of treatment?
   Yes
   No (if no then please skip Q2)

2. In your clinical practice, what is the follow-up duration you advice to Typhoid patients after completion of treatment?
   1 month
   2 months
   3 months

3. Comparatively which type of cases are more reported in your clinical practice
   Relapse
   Resistance

4. What is your observation regarding a relapse patient, do they comply with the advised duration of therapy (10-14 days)?
   Always
   Most of the time
   Occasionally
   Never

5. In your clinical practice, when a relapse patient comes after discontinuation of therapy?
   1 week
   2 weeks
   3 weeks or more

6. How much typhoid infection affects the patient's overall quality of life during treatment?

Not at all	A little	Moderate	Very Much
1	2	3	4

7. In your clinical practice, which of the following complications mostly reported in long term by the patients treated for Typhoid?

Gastrointestinal	Neuropsychiatric	Respiratory	Cardiovascular
Intestinal hemorrhage	Disorientation	Cough	ECG Changes (Nonspecific)
Perforation	Delirium	Pneumotyphoid	Tachycardia
	Convulsions	Ulceration of posterior pharynx	Weak Pulse
			Hypotension

Which topic you want us to discuss in TIMES volume 3 (Please tick one, the most important you consider)

   Treatment options for Typhoid
   Risk Factors for Typhoid
   Relapse of Typhoid
   Complications related to the disease
   Managing the side effects during and post treatment

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