Emerging antibiotic resistance in bacteria with special reference to India

D Raghunath

Sir Dorabji Tata Centre for Research in Tropical Diseases, Innovation Centre, Indian Institute of Science Campus,
Bangalore 560 012, India

(Fax, 91-80-23466006; Email, sdtc265iisc@vsnl.net)

The antibiotic era started in the 1940s and changed the profile of infectious diseases and human demography. The burgeoning classes and numbers promised much and elimination of this major cause of human (and animal) morbidity appeared possible. Bacterial antibiotic resistance which was observed soon after antibiotic introduction has been studied extensively. Diverse mechanisms have been demonstrated and the genetic basis elucidated. The resilience of the prokaryote ecosystems to antibiotic stress has been realized. The paper presents these subjects briefly to afford an overview. The epidemiology of antibiotic resistance is dealt with and community practices in different countries are described. The role of high antibiotic usage environments is indicated. The implication of the wide use of antibiotics in animals has been pointed out. Steadily increasing antibiotic resistance and decreasing numbers of newer antibiotics appear to point to a *post-antibiotic period* during which treatment of infections would become increasingly difficult. This article attempts to review the global antimicrobial resistance scene and juxtaposes it to the Indian experience. The prevalence in India of antibiotic resistance among major groups of pathogens is described. The factors that determine the prevalent high antibiotic resistance rates have been highlighted. The future research activity to ensure continued utility of antibiotics in the control of infections has been indicated.

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1. Introduction

The discovery of antibiotics in the 20th Century marked a watershed in the treatment of infections. The ability to treat the serious infections of the pre-antibiotic era stimulated advances in medical fields and enlarged the scope of medical care. However, while a drastic change has taken place in the causes of fatal infections, they are still a major cause of death the world over (World Health Report 2003). While demographic changes and drug access issues are important reasons in the developed and developing worlds, respectively, "relentless and Dizzying Rise of Antimicrobial Resistance" (Nordberg *et al* 2004) has contributed in a large measure to the persistence of infections as a major cause of morbidity and mortality.

The rapid emergence of resistance to antibiotics amongst pathogens generates visions of the 'potential post-antibiotic era threatening present and future medical advances' (Wise 2008). In addition, the spectacular success of antibiotics generated a complacency in the 1960s and 1970s exemplified by the (now surprising) statement by William H Stewart, US Surgeon General that "[it] is time to close the book on infectious diseases" (Stewart 1967). This attitude resulted in a relative neglect of infection related issues in the 1960s and 1970s. The HIV/AIDS pandemic as well as emergent and reemergent infections have rekindled the interest in infectious diseases but the antibiotic scene remains subdued (Nordberg *et al* 2004). The steady discovery of novel antibiotics in the period 1940 – 1980 has not been sustained. The 1990s saw only one new antibiotic class viz the oxazolidinones joining

Keywords. Antibiotic modifying enzymes; antibiotic resistance; antimicrobial; epidemiology; plasmids/transposon/integron; post-antibiotic era

Abbreviations used: CA-MRSA, community-associated methicillian-resistant *Staphylococcus aureus*; LRTI, lower respiratory tract infection; MDR, multidrug resistant; MIC, minimum inhibitory concentration; MOTT, mycobacteria other than tuberculosis; URT, upper respiratory tract; VRE, Vancomycin-resistant enterococci

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Figure 1. Utility of antibiotics over the years – a schematic pitcture. (Reproduced from Nordberg *et al* (*loc. cit*))

point mutations and gene amplifications whereas horizontal transfer of resistance genes between bacteria within and across species by transposons, integrons or plasmids are extrinsic mechanisms, the resultant gene pool responds to the introduction of novel antibiotics by generating resistance determinants which are freely exchanged (Livermore 2004). Once this has happened restriction of the use of antibiotic would not result in decrease of resistance.

Genetic changes reflect phenotypic alleles, and enable the bacteria to deal with the antibiotic. These mechanisms can be summarized as follows:

- *Antibiotic inactivating enzymes* e.g. *β*-lactamases, aminoglycoside modifying enzymes, chloramphenicol acetyl transferase etc.
- *Impaired uptake of antibiotics* which can be natural due to cell envelope characteristics. In the case of acquired resistance changes in porins may interfere with antibiotic transport.
- *Drug efflux* may be the operative mechanism in some cases. Mutations result in over expressions in some cases.
- Modification of the target resulting in less avid binding of the antibiotic is the mechanism seen commonly in *β*-lactam resistance in gram positive organisms *e.g. Streptococcus pneumoniae* and *S. aureus*. An extreme example due to ribosomal modification that makes streptomycin resistant organisms use the antibiotic as a growth factor.
- Development of an *alternate metabolic pathway* would allow the bacteria to grow in the presence of the antibiotic. This mechanism is seen in glycopeptide, aminoglycoside, macrolide, sulpha/trimethoprim resistance amongst others.

A detailed description of the mechanisms is beyond the scope of this article, however, it is worthwhile noting that in many instances more than one mechanism is in operation e.g.

in acquired resistance in Gram-negative bacteria antibiotic modifying enzymes, permeability barriers, enhanced efflux and ribosomal modification operate simultaneously to varying extent (Streulens 2003).

3. Epidemiology

The burgeoning literature on antimicrobial resistance in the post-antibiotic years, particularly in the recent decades tends to convey the impression that the phenomenon is recent. A study of the microbial world would impress that "antibiotics are old-established natural products that have had common, but changing and manifold, physiological uses throughout evolutionary time" even as far back as the 'RNA world' (Chadwick *et al* 1992), which probably was the forerunner of the present DNA world. The extensive use of antibiotics in medicine and agriculture has increased the reservoir of resistance genes. It is thus not surprising that the introduction of a new agent is, practically invariably, followed by heightened resistance. Legitimately used antibiotic therapy based on sound evidences is justified, however, the inappropriate use largely exceeds this and introduces a large amount of antibiotic into the environment (Wise *et al* 1998). There is a wide variation in the prescribing habits in different countries. Thus there is a four fold variation between Netherlands and France. The lower consumption of antibiotics translates to lower resistance levels, figure 2 illustrates this as regards penicillin resistance in pneumococci (Albrich *et al* 2004).

It is noteworthy that the lower antibiotic usage in the Netherlands has not affected the dynamics of infectious diseases in the country. The most often inappropriately treated community infection is that of the upper respiratory tract (URT). Viral URT infections do not need antibiotic therapy but are not readily distinguishable from those that do, due to lack of readily available cost effective laboratory tests. The "to be sure" attitude of the treating physician and (often) patient pressure are other causes of the practice. Once antibiotic treatment has been started the duration is ill defined. Obviously the shorter the treatment course the less the antibiotic stress in the environment (Rice 2008).

Antibiotics are used as growth promoters, prophylactics and therapeutic agents in veterinary medicine. It is estimated that this use equals that used in medicine. This largely uncontrolled field adds to the antibiotic selection pressure. This has resulted in the breeding of multi-drug persistent pathogens in hospitals and community as well as breeding resistant organisms of veterinary importance (Hubert *et al* 1991). These aspects are well highlighted (World Health Organization 2002). Certain areas in hospitals like ICUs and areas with immunosuppressed and debilitated patients as well as treatment modalities like topical and

prophylactic use of antibiotics are foci of generation of multidrug resistant (MDR) bacteria. Gradual dissemination to the community through population interaction spreads the organisms widely (Streulens 2003). Over the years bacterial populations undergo changes in their antibiotic susceptibility which may be foreseen considering changes in antibiotic prescribing practices. Thus the spurt in MDR *S. typhi* that took place in the last years of the 1980s caused a change in treatment protocols. From 1988 fluoroquinolones became the favoured first choice drugs for the treatment of enteric fever and chloramphenicol was not prescribed. Gradually chloramphenicol sensitivity has returned to levels that make the drug a viable option (Kapila 2008). Similarly the earliest experiences with MRSA (Barber 1961) did not anticipate the centre stage that the organisms would take (Arakere *et al* 2005).

There is therefore a strong case for continued surveillance at all levels, the hospital, city/region, country and supra-national levels. It is only then the ramifications of problem can be learnt. Such mechanisms are in position in the industrialized countries but the developing world (including India) is an enigma (Stewart 1967; World Health Organization 2002). Figure 3 summarizes the epidemiology of antibiotic resistance.
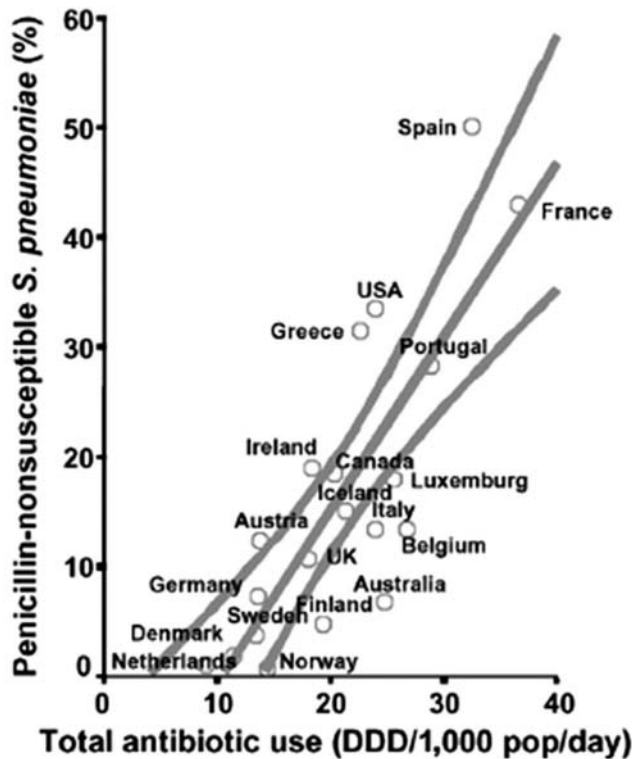
4. Antibiotics in the community

Infectious diseases continue to be a leading cause of mortality the world over, more so in developing countries with poorly accessed health services (World Health Report 2007). Over all the burden of bacterial infections is rising, largely fuelled by antibiotic resistant organisms. However, except for MDR *Mycobacterium tuberculosis*, precise quantitation and trend analysis is sketchy. This challenging task has been initiated but there is a long way to go. The Indian scene is no better since large parts of country do not have the technical infrastructure to generate useable data on the ground. While newer drugs have kept the problem under control, the poorer communities are squeezed between rampance resistant and inadequate resources. Thus, the contribution of infectious diseases to overall mortality is greater in impoverished societies.

The evolution of CAMRSA and its spread even in developed countries is an example of the public health impact of the resistance problem (Herold *et al* 1998).

Apart from the medical consequences of antibiotic resistance there is a direct cost to society. Newer antibiotics come with a higher cost, implementing hospital practices to control spread of resistant bacteria and investigation of outbreaks add to the cost of health care. On a national scale the burden is considerable amounting to about £ (Stg) 1,000 million per annum in the UK and corresponding figures in other countries that have computed their costs. (Plowman *et al* 2001). A European computation of the cost of blood stream infections caused by MRSA revealed that the single pathogen cost more than 117 million euros a year exceeding the research grants to study antimicrobial research for 1999-2002 (Nordberg *et al* 2004).

The prolific discovery of antibiotics that changed the bacterial infection scenario has slackened considerably. After the 1970s only one novel class of antibiotic--the oxazolidinones has been added, all other introductions

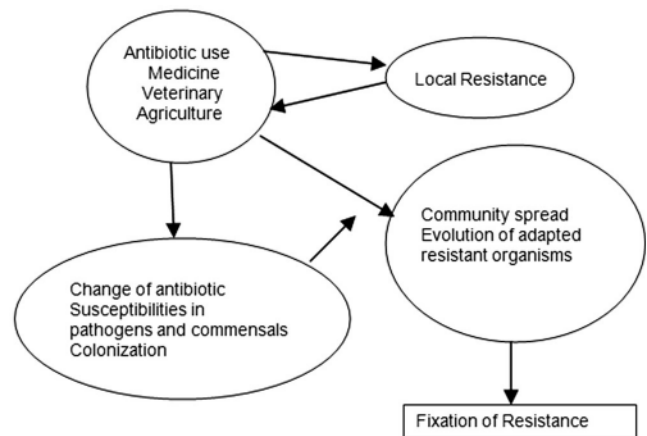**Figure 2.** Relationship of National antibiotic usage and resistant *S. pneumoniae*.

Figure 3. Broad epidemiology of antimicrobial resistance.

have been modifications of current antibiotic classes. These modified agents suffer from the disadvantages of the parent molecules (Greenwood 2003). The major reason for this has been the down scaling of R&D in the field by major pharmaceutical companies. Due to low returns and poor net present value (NPV) research efforts got diverted to the management of chronic diseases (Reed *et al* 2002).

It is clear from the material presented that despite a significant increase in antibacterial agents, infections are here to stay and the euphoria of the early years has given place to a sober appraisal. The phenomenon of resistance is seen in more complex parasites e.g. fungi, protozoa and parasites. There is therefore a very strong motivation to address the problems and aim to conserve our resources (Wise 2008).

5. Control of antimicrobial resistance

In essence all strategies aim at optimizing the antibiotic stress in the environment, decrease unintended interaction between antibiotics and pathogens, restrict the spread of resistant organisms and treat infections with the minimum amount of antibiotic necessary to effect cure. Towards this end a number of countries have evolved national programmes that tackle the complex issue. The common methods being focused on are (Carbon *et al* 2002):

- Surveillance of antibiotic use and resistance rates.
- Optimizing antibiotic use with treatment guidelines.
- Education of professionals and the public.
- Prevention with infection control measures and immunization.
- Industry involvement, financial resource mobilization and drug development.
- Regulatory issues with central prescribing restrictions and advertising restrictions.
- Audit with evaluation of interventions, audit of compliance and physician feed back.
- International cooperation.

The objective will be successful if a common infection like a cold is precisely diagnosed and treated with the right antibiotic for the shortest time to ensure eradication of the bacterial infection when it occurs. We have a long way to go before we achieve this seemingly simple objective even in industrialized affluent countries. In India, as in other developing countries, we have not taken the initial steps. Antimicrobial resistance is a major emerging infection and needs to be tackled as much.

6. The Indian scene

The Indian scene is particularly grim due to various factors. The high speed of acquisition of resistance as exemplified by cotrimoxizole resistance already referred to. Generally, there is little control on the use of antibiotics. Community awareness of the issues involved in antibiotic therapy is poor and this is compounded by over-the-counter availability. Coupled with primitive infection control in hospitals and weak or deficient sanitation, the conditions are suited for transmission and acquisition of antibiotic resistance. The facility with which enteric pathogens spread widely in India illustrates this point. On the other hand countries with a good sanitary infrastructure are hardly bothered by the import of cholera cases (Nair 2007). While newer, costlier drugs where available have largely kept pace clinically, the poorer communities are squeezed between rampant resistance and inadequate resources. Large parts of the country do not have the technical infrastructure to generate useable data on the ground. Thus, the contribution of infectious diseases is greater in impoverished societies.

In the absence of a Central Monitoring Agency the national scene in India with regard to antimicrobial resistance is not known. The two probable exceptions are *M. tuberculosis* and *Leishmania donovani*. The former has been studied consistently by the Tuberculosis Research Centre, Chennai, National Tuberculosis Institute, Bangalore and National JALMA Research Institute, Agra (Paramasivam 1998). *L. donovani* has reemerged in a limited geographic area and the intense interest has documented the evolution of drug resistance in the pathogen (Jha 2006).

With the advent of oral rehydration therapy infant mortality due to diarrhoeal diseases has decreased to levels below that due lower respiratory tract infection (LRTI) which is now the leading cause in this population. The most important pathogen causing bronchopneumonia is *Streptococcus pneumoniae* and a syndromic antibiotic therapy is being used to control the mortality (Lalitha 2008). This approach would be effective only if the pneumococcus remains sensitive to the drugs used in the programme. However, the results of a carriage study in North India (Jain 2005) appear reassuring as far as penicillin resistance but alarming as regards co-trimoxazole resistance - the drug used for syndromic treatment. This is supported by the study of Goyal *et al* (2007). Antibacterial resistance in *S. pneumoniae* has now become a global phenomenon, particularly in India's immediate neighbourhood (Jae-Hoon Song *et al* 2004). Except for a high degree of resistance to cotrimoxazole, the Indian and Nepalese strains have retained their sensitivity to the penicillins, macrolides and fluoroquinolones (Lalitha 2008). It remains to be seen if the widespread use of antibiotics in syndromic control of LRTI changes the pattern over time.

Haemophilus influenzae is not often isolated by microbiological laboratories and the extent of morbidity caused by the organism is not known. Therefore, resistance issues are not raised. However, the carriage

rate surveys in north India warn of the high prevalence of ampicillin-resistant *H. influenzae* in school going children. Strengthening diagnostic capacity in this area is need (Jain 2006).

6.1   *Enteric pathogens*

Vibrio cholerae has acquired resistance to a number of antimicrobials. The resistance spectrum varies in different locales. This makes it necessary to know the local pattern if antimicrobials are to be used. Thus in the area around Delhi extensive resistance to furazolidone, cotrimoxazole and nalidixic acid was noted while tetracycline remained effective (Sharma *et al* 2007). On the other hand in Bangladesh tetracycline resistance was also seen frequently (Saha *et al* 2006).

Coliforms have changed their susceptibility patterns extensively. Coliform: *β*-lactam resistance is widespread due to vertical as well as horizontally acquired resistance factors. All the known generation of *β*-lactamases are actively circulating. Most tertiary care hospitals are faced with extensive resistance problems in their *Escherichia coli* and *Klebsiellae*. Other multiresistant enterobacteriae too establish themselves (Rodrigues *et al* 2004; Shukla *et al* 2004; Baby Padmini and Appalaraju 2004; Kumar *et al* 2006; Gupta *et al* 2006; Arora *et al* 2007; Jain and Mandal 2007; Wattal 2008).

The horizontal spread of resistance factors into environmental gram negative bacteria has seen the emergence of multidrug resistant *Acinetobacter*, *Pseudomonas*, *Serratia*, *Stenotrophomonas* sp wherever looked for, even in (Prashant and Badrinath 2004; Sinha and Srinivasa 2007; Yavankar *et al* 2007) skin carriage strains. This is a part of a worldwide phenomenon. The current concept as far as *Acinetobacter* infections is described and typical of the other organisms of this type (Munoz-Price and Weinstein 2008).

Enteric fever causing *S. typhi* and *S. paratyphi* A have had a fascinating evolution. Till 1987 low level resistance was seen in them but the infections could be treated with the three front line drugs ampicillin, chloramphenicol and cotrimoxazole (Raghunath and Kher 1989). In 1988 there was a dramatic shift in resistance resulting in the fluroquinolones becoming the drugs of choice (Anand *et al* 1990). By the start of 1990s chloramphenicol resistance was the rule (Pillai and Prakash 1993; Sen *et al* 2007). Since that time there has been a restitution of chloramphenicol sensitivity and increase in fluoroquinolone resistances (Das and Bhattacharya 2006).

Shigellae, in particular *S. dysenteriae* type 1 the causative organism of epidemic bacillary dysentery, have been notorious in becoming resistant to successively introduced antibacterials. Strains resistant to all enterically administered antibacterials have been reported. The infection, occurring in previously disadvantaged children has been a major problem (Niyogi *et al* 2001). The picture described in Western Nepal (Wilson *et al* 2006) is similar to the Indian scenario.

Amongst the bacteria causing *sexually transmitted diseases* there has been a change in the antibiotic susceptibility of *Neisseria gonorrhoeae,* Penicillin resistance and fluoroquinolone resistance is widespread. Alternate drugs like azithromycin and the third generation cephalosporins have to be used (Ray *et al* 2006; Khaki *et al* 2007). There has been little work in India on antibiotic susceptibility of other STD agents. There is no report of penicillin resistance in *Treponema palladium*.

Neisseria meningitidis the causative agent of sporadic and epidemic meningitis too has shown resistance to penicillin occasionally (Manchanda *et al* 2006; Singhal *et al* 2007).

6.2   *Gram-positive cocci*

6.2.1 *Streptococci other than* S. pneumoniae: *S. pyogenes* continues to be sensitive to penicillin but resistance to tetracyclines and macrolides have been encountered. Interaction with Indian medical microbiologists reveals that few laboratories routinely test their isolates for their antibiotic susceptibilities. Those who do, have encountered varying degrees of tetracycline and macrolide resistance ranging upto 40% in both classes. (Personal communications) There is however a case for reappraisal of these beliefs (Capoor *et al* 2006). Groups B and G streptococci probably have a more diverse resistance pattern.

Staphylococcus aureus has developed resistance to newer antibiotics over the years. Methicillin resistance is quite frequent approaching and at time exceeding 50% in tertiary care centres. Vancomycin resistance has been very low. However, the reckless use of the antibiotic may alter the scenario. This coupled with the emergence of CA-MRSA would pose serious clinical problems with global ramifications (Arakere *et al* 2005; Nadig 2006). Likewise coagulase negative staphylococci have acquired multiple resistance and become important nosocomial pathogens (Singhal *et al* 2006).

VRE are being isolated in Indian hospital laboratories that look for them. Tertiary care centres see varying numbers. Thus one centre in north India 38% of blood culture isolated enterococci from Intensive Care Unit patients were vancomycin resistant (Wattal 2008). On the other hand another centre in western India "does not have a problem with VRE". (C Rodrigues, personal communication). Two other studies examined 52 and 685 enterococcal isolates (Karmarkar *et al* 2004; Ghoshal *etal* 2006). In the former study 12 isolates (53%) of VRE of the van B type were seen, in the latter study from north India a low level of resistance

(1.4%) was reported. Thus the VRE problem does exist but in a variable manner in the hospital environment. The experience of Prakash *et al* (2005) shows the issue is more complex. There is an impression that control on vancomycin prescriptions keeps the VRE rates low. This requires confirmation.

6.3 *Mycobacteria*

M. tuberculosis has become resistant to successively introduced antibacterial agents. The combined resistance to isoniazid and rifampicin (multi-drug resistance) impacts strongly on control programmes. There has been a steady rise in such strains in treatment of naïve patients (Jesudasan *et al* 2003; Ramachandran and Narayanan 2008). The additional acquisition of resistance to a fluroquinolone and one of three injectable second line drugs (capreomycin, kanamycin, amikacin) has defined the Extensively Drug Resistant (XDR) tuberculosis. Such strains have been encountered regularly in HIV and non HIV infected individuals. They have had a large negative impact on control programmes (Rodrigues 2008).

M. leprae has become resistant to "various concentrations" of dapsone, rifampicin or clofazimine with 6.23% being resistant to two drugs. This has resulted in the establishment of multi-drug regime for the control of the disease. With multi-drug resistant organisms being described the long term prospects are not too good (Ebenezer *et al* 2002; Scollard *et al* 2006). The HIV/AIDS epidemic has kindled interest in mycobacteria other than tuberculosis (MOTT). Reports on the isolation of MOTT strains have appeared in literature. In a systematic study of *Myco avium* extensive resistance was noted (Venugopal *et al* 2007).

6.4 *Protozoa*

Plasmodium falciparum has become resistant to chloroquin and other anti-malarials successively. Only the recently introduced artemesinine derived drugs are uniformly effective (Mohanty *et al* 2006). *P. vivax* remained sensitive to antimalarials for a long time. However, reports of emerging resistance have been made (Murphy *et al* 1993).

L. donovani has become resistant to the pentavalent antimonials, meglumine antimoniate and sodium stibogluconate. Likewise, pentamidine unresponsiveness, as well as its toxicity, has removed another therapeutic option. Amphotericin B, paramomycin and the recently introduced miltefosin are available but often unaffordable but are being used extensively in a programme mode (Jha 2006).

Entamoeba histolytica has shown some drug resistance but the problem does not seem serious (Bansal *et al* 2006).

Two other protozoa of importance are *Giardia lamblia* and *Toxoplasma gondii*. They have assumed greater

importance due to their enhanced pathogenicity in HIV infected individuals. The treatment has been quite successful but the prophylactic use of the useful drugs must stimulate resistance.

In summary, this brief review highlights the extensive problem of antimicrobial resistance encountered in India. It also emphasizes the need for systematic programmes to address the problem and evolve an antibiotic conservation practice, particularly, for the killer diseases such as tuberculosis, Kala azar, malaria, etc.

7. The future

It is probably, not premature to explore other methods of treating resistant bacterial infections. Some of these are given below.

7.1 *Vaccines*

The reduction of the number infected due to a pathogen will decrease bacterium/antibiotic interaction and thereby genesis of resistant strains. The salutary experience of the introduction of multivalent pnemococcal conjugate vaccine in pediatric practice is a pointer (Whitney and Klugman 2004). Not only fewer infections were seen but colonization and dissemination of the pathogens was observed. Likewise the sharp decline in *Haemophilus influenzae* infections after introduction of the type B conjugate vaccine supports this strategy. The use of the viral influenza vaccine has decreased the number of fatal secondary bacterial infections and thereby the quantum of antibiotic usage in the vaccinated group.

The partial success of a polysaccharide vaccine against *S. aureus* in preventing blood invasion during dialysis (Falton *et al* 2004) opens up an alternate therapy for the dreaded MRSA with glycopeptide resistance. Genome based studies and the opportunities opened up by DNA vaccine technology are targeting a number of organisms ranging from plague causing *Yersinia pestis* to uropathic *E. coli* (Rappuoli and Coracci 2003). If these attempts fulfill their promise considerable decrease in antibiotic usage in the community can be achieved. This is a field worth pursuing.

7.2 *Bacteriophage*

The specific targeting and efficient elimination of bacteria by their bacteriophage has interested clinicians. Some success was achieved in the 1920s and 1930s, however, the advent of sulphonamides and antibiotics relegated the phage technology to the background. The looming failure of antibiotics may give the subject a fillip (British Broadcasting Corporation, Accessed 8th May 2008). There is a potential to

develop these agents for medical/veterinary use. In the latter case they have been tried to remove animal commensals which are human pathogens like enterohaemorrhagic *E.coli* (EHEC) or *Campylobacter* (Carillo *et al* 2005).

Alternate systems of medicine have been current in indigenous communities. The preparations used by these systems have made claims (at times tall) that would probably draw attention when treatment options dwindle. Likewise, the use of *probiotics* particularly in managing gut flora may offer an option.

7.3   *Diagnostics*

Antibiotics used specifically and for the right period are least likely to generate resistance. Advanced diagnostics are needed to achieve this. The case of common cold has already been mentioned. There would be many more instances. What is sought by a clinician is information on existing infection, its aetiology, the antibiotic susceptibility of the pathogen and information on the clearance of the infection. Technology for this is existent but not rapid enough to be clinically useful. Thus the introduction of the rapid test to detect *S. pyogenes* form throat swabes has decreased inappropriate antibiotic administration significantly (Contessobto *et al* 2000).

8.   **Summary**

It has now become evident that the huge optimism of the 1950s and 1960s of infections becoming insignificant has been misplaced. The microbial world has demonstrated remarkable resilience and the emergence of resistance is practically invariable upon the introduction an antibiotic into the environment. The relentless build-up of resistances may make the valuable antibiotic assets useless and a post-antibiotic scenario may emerge. There are enough resources at least in the developed world to treat their infections but the developing world is facing access issues and contributing to the resistance pool. The problem, therefore, is global and requires to be tackled on that scale.

It is for the biological community to accept this as 'A Time of Challenge and Opportunity'. International agencies like the European Commission and WHO have enumerated strategic plans as follows (World Health Organization 2002):

- Public and professional education towards rational use of antimicrobials.
- Coordination of surveillance of antibiotic resistance and antibiotic use in human and animal health sectors.
- Refined regulation of antibiotic registration for use in both sectors.
- Development and evaluation of improved diagnostic methods.

- Promotion and evaluation of medical and veterinary guidelines.
- Restriction of antibiotic use as growth promoters in good animals.
- Promotion of infection control practice in health care institutions.
- Development of novel antimicrobial drugs and vaccines.
- Closer international cooperation.

The Indian scene in this regard is dismal. Some of the practices are in place in some institutions but the community, regions and nation are largely unaware of the issues. It is time that a National effort is initiated to tackle these problem of antimicrobial resistance which can have disastrous effects on our population.

References

Albrich W C, Monnet D L and Harbarth S 2004 Antibiotic Selection Pressure and Resistance in *Streptococcus pneumoniae* and *Streptococcus pyogenes*; *Emerging Infect. Dis.* **10** 514–517

Anand A C, Kataria V K, Singh W and Chatterjee S K 1990 Epidemic multiresistant enteric fever in eastern Indian; *Lancet* **335** 352

Andersson D I and Levin B R 1999 The biological cost of antibiotic resistance; *Curr. Opin. Microbol.* **2** 489–493

Arakere G, Nadig S, Swedberg G, Macaden R, Amarnath S K and Raghunath D 2005 Genotyping of Methicillin – Resistant *Staphylococcus aureus* strains from two hospitals in Bangalore, South India; *J. Clin. Microbiol.* **43** 3198–3202

Arora S, Saha S and Bal M 2007 Imipenen-resistance among multi-drug resistant clinical strains in urinary infections from Kolkata; *Indian J. Med. Res.* **125** 689–691

Austin D J and Anderson R M 1999 Studies of antibiotic resistance with in the patient, hospitals and the community using simple mathematical models; *Philos. Trans. R. Soc. London B. Biol. Sci.* **354** 721–738

Baby Padmini S and Appalaraju B 2004 Extended spectrum βlactamases in urinary isolates of *Escherichia coli* and *Klebsiella pneumoniae* prevalence and susceptibility pattern in a tertiary care hospital; *Indian J. Med. Microbiol.* **22** 172–174

Bansal D, Sehgal R, Chawla Y, Malla N and Mahajan R C 2006 Multi-drug reistance in amoebiasis patients; *Indian J. Med. Res.* **124** 189–194

Barber M 1961 Methicillin-resistant staphylococcus; *J. Clin. Pathol.* **14** 385–393

British Braodcasting Corporation:'Red Army' virus to combat MRSA by Clare Murphy available at *http://news.bbc.co.uk/1/hi/health/6943779-stm* accessed: 8th May 2008

Capoor M R, Nair D, Deb M, Batra K and Aggarwal P 2006 Resistance to erythromycin and rising penicillin MIC in *Streptococcus pyogenes* in India; *Jpn. J. Infect. Dis.* **59** 334–336

Carbon C, Cars O and Christiansenle 2002 Moving from recommendation to implementation and audit: Part I, Current

recommendations and programsL: a critical commentary; *Clin. Microbiol. Infect. (Suppl. 2)* **8** 92–106

Carillo C L, Atterbury R J, El-shiring A, Connerton P L, Dillon E, Scott A and Connerton I F 2005 Bacteriophage therapy to reduce Campylobacter Jejuni colonization of Broiler chickens; *Appl.Environ. Microbiol*. **71** 6554–6563

Chadwick D, Whelan J and Widdow K 1992 Secondary metabolites: their function and evolution; in *Secondary metabolites: Their function and evolution* (eds) D Chadwick, J Whelan and K Widdows K (Ciba Foundation Symposium 171) (Chichaster: John Wiley)

Contessobto S C, Camara S M, Avniks M J, Ojed A, Eanriet J M, Cascales B I and Rodrigues S F 2000 Rational use of antibiotics in paediatrics; impact of a rapid test for detection of beta-haemolytic group. A Streptococci in acute pharynglotitis; *An. Esp. Pediatr*. **52** 212–219

Darwin C 1859 *On the origin of species by means of natural selection* (London Murray) Accessed at *http://www.literature.org/authors/drawin-charles/the-origin-of-species/*

Das U and Bhattacharya S S 2006 Antibiogram, phage typing and biotyping of *Salmonella Typhi* and *Salmonella paratyphi* A from Rourkela, Orissa; *Indian J. Med. Res*. **124** 109–111

de Bruin M A and Rilay L W 2007 Does vancomycin prescribing intervention affect vancomycin-resistant enterococcus infection and colonization in hospitals? A systematic review; *BMC Infect. Dis*. **7** 24 (Accessed: *http://www.biomedcentral.com/*1471-2334/7/24 11 pages)

Ebenezer G J, Norman G, Joseph A, Daniel S and Job C K 2002. Drug resistant *Mycobaterium leprae* – results of mouse footpad studies from a laboratory in south India; *Indian J. Lepr*. **74** 301–312

Enright M C, Robinson D A, Randle G, Feil E J, Grundmann H and Spratt B G 2002 The evolutionary history of methicillin-resistant *Staphylococcus aureus* (MRSA); *Proc. Natl. Acad. Sci. USA* **99** 7687–7692

Falton A I, Horwith G, Fuller S, Propst M and Nasco R. 2004 Development of Staph VAX, a poly saccharide conjugate vaccine against *S.aureus* infection from lab bench to phase III clinical trials; *Vaccine* **22** 880–887

Ghoshal U, Garg A, Tiwari D P and Ayyagiri A 2006 Emerging vancomycin resistance in enterococci in India; *Indian J. Pathol. Microbiol*. **49** 620–622

Goyal R, Singh NP, Kaur M and Talwar V 2007 Antimicrobial resistance in invasice and colonizing *Streptococcus pneumoniae* in North India; *Indian J. Med. Microbiol*. **25** 256–259

Greenwood D 2003 Historical introduction; in *Antibiotic and chemotherapy* 8th editions(eds) R G Finch, D Greenwood and R S Norrby (Edinburgh: Churchill Livingstone) pp 3–10

Gupta E, Mohanty S, Sood S, Dhawan B, Das B K and Kapil A. 2006. Emerging resistance to carbapenemns in a tertiaty care hospital in north India; *Indian J. Med. Microbiol*. **124** 95–98

Harbarth S, Cosgrove S and Carmeli Y 2002 Effects of Antibiotics on Nosocomial Epidemiology of Vancomycin-Resistant Enterococci; *Antimicrob. Agents Chemother.* **46** 1619–1628

Herold B C, Immergluck L C, Maranan M C, Laudadale D S, Gaskin R E, Boyle-Vauna S, Leiteh C D and Danm R S 1998 Community acquired Methicillin-resistant *Staphylococcus*

aureus in children with no identified predisporing rish; *JAMA* **279** 593–598

Hubert Ph.E, Gijs J R, Bert vank, Wim H J, Tanny vander R and Monton R P 1991 Quinolone resistance in Camphylobacter isolated from man and poultry following introduction of fluroquinolones in Veterinary medicine; *J. Antimicrob. Chemother*. **27** 199–208

Jae-Hoon S, Sook-In J, Kwan S K, Na Y K, Jun S S, Hyun-Ha C, Hyun K K, Won S O *et al* 2004 High prevalence of antimicrobial resistance among clinical *Streptococcus pneumoniae* isolates in Asia (an ANSORP study); *Antimicrobiol. Agents Chemother*. **48** 2101–2107

Jain A, Kumar P and Awasthi S 2005 High nasopharyrgal carriage of drug resistant *Streptococcus pneumoniae* and *Haemophilus influenzae* in North Indian school children; *Trop. Med. Int. Health* **10** 234–239

Jain A, Kumar P and Awasthi S 2006 High ampicillin resistance in different biotypes and serotypes of *Haemophilus influenzae* colonizing the nasopharyrox of healthy school-going Indian Children; *J. Med. Microbiol*. **55** 133–137

Jain A and Mandal R 2007 Prevalence of antimicrobial resistance pattern of extended spectrum *β*-lactamase producing *Klebsiella* spp isolated from cases of neonatal speticaemia; *Indian J. Med. Res*. **125** 89–94

Jesudasan M V, Mukundan U, Saaya R, Vanitha K and Lalitha M K 2003. Resistance of *Mycobacterium tuberculosis* to the first line anti tubercular drugs – a twenty year review; *Indian J. Med. Microbiol*. **21** 127–128

Jha T K 2006 Drug unresponsiveness and combination therapy for Kala Azar; *Indian J Med Res*. **123** 389–398

Kapila K 2008. The Saga of Antibiotic Sensitivity in *Salmonallae* over the last sixteen years: A Report from Department of Microbiology, AFMC, Pune, Maharashtra:; in *Proceedings of the 9th Sir Dorabji Tata Symposium* Bangalore (India) 10 -11 March 2008 (in press)

Karmarkar M G, Gershom E S and Mehta P R 2004 Entero-coccal infection with special reference to phenotypic characterization and drug resistance; *Indian J. Med. Res. (Suppl.)* **119** 22–25

Khaki P, Bhalla P, Sharma A and Kumar V 2007 Correlation between *in vitro* susceptibility and treatment outcome with azithromycin in gonorrhoea: A prospective study; *Indian J. Med. Microbiol*. **25** 334–337

Kumar M S, Lakshmi V and Rajagopalan R 2006 Occurence of extended spectrum, *β*lactamases among *Enterobacteriaceae* spp isolated at a tertiary care institute; *Indian J. Med. Microbiol*. **24** 208–211

Lalitha M K 2008. Antibiotic Resistance among *Streptococcus pneumonaie;* in *Proceedings of 9th Sir Dorabji Tata Symposium* (eds) C Durga Rao and D Raghunath (in press)

Leclerq R, Detlot E, Duval J and Courvalin P 1988 Plasmid-mediated resistance to vancomycin and teicoplanin in Enterococcus faecium; *N. Engl. J. Med*. **319** 157–161

Lipsitah M, Bergstrom C T and Levin B R 2000 The epidemiology of antibiotic resistance in hospitals: paradoxes and prescriptions; *Proc. Natl. Acad. Sci. USA* **97** 1938–1943

Livermore D 2004 Can better prescribing turn the tide of resistance?; *Nat. Rev. Microbiol*. **2** 73–78

Madeinos A A 1997 Evolution and dissemination of betalactamases accelerated by generation of beta lactum antibiotics; *Clin. Infect. Dis*. **29** 1419–1422

Manchanda V, Gupta S and Bhalla P 2006 Meningococcal disease: History, epidemiology, pathogenesis, clinical manifestations, diagnosis, antimicrobial susceptibility and prevention; *Indian J. Med. Microbiol*. **24** 7–19

Martinez – Martinez L, Pascnal A and Jacoby G A 1998 Quinolone resistance from a transferable plasmid; *Lancet* **351** 797–799

Mohanty S, Patel D K, Pati S S and Mishra S K 2006 Adjuvant therapy in cerebral malaria; *Indian J. Med. Res*. **124** 245–260

Murphy G.S, Basrilt, Purnomo, Anderson E M, Bangs M J, Mount D L *et al* 1993 Vivax malaria resistant to treatment and prophylaxis with chloroquine. *Lancet* **341** 96–100

Murray B E 2000 Vancomycin-Resistant Enterococcal Infections; *N. Engl. J. Med*. **342** 710–721

Munoz-Price L S and Weinstein R A 2008 Acinetobacter Infection in current concepts; *N. Engl. J. Med*. **358** 1271–1281

Nadig S, Namburi P, Raghunath D and Arakere G 2006. Genotyping of Methicillin resistant *Staphylococcus aureus* isolates from Indian hospitals; *Curr. Sci*. **91** 1364–1359

Nair G B 2007 How much more research is required to prevent cholera?; *Indian J. Med. Res*. **125** 612–614

Niyogi S K, Mitra U and Dutta P 2001 Changing pattern of serotypes and antimicrobial susceptibility of *Shigella* species isolated from children in Calcutta; *Jpn. J. Infect. Dis*. **54** 121–122

Nordberg P, Monet D L and Cars O 2004 Background document for WHO project: Priority Medicines for Europe and the World "A Public Health approach to Innovation". Accessible *http://mednet3.who.int/priorityneeds/*

Paramasivam C N 1998 An overview of drug resistant tuberculosis in India; *Indian J. Tubercul*. **45** 73–81

Pietersberg W 2001 Endogenoms Antimicrobial Molecules: An Ecological Perspective, Chapter 25

Pillai P K and Prakash K 1993 Current status of drug resistance and phage types of *Salmonella typhi* in India; *Indian J. Med. Res*. **97** 154–158

Plowman R , Graves N, Griffin M A, Roberts J A, Swan A V, Cookson B and Taylor L 2001 The rate and art of hospital acquired infections occurring in patients admitted to selected specialities of a District General hospital and the national burden imposed; *J. Hosp. Inf*. **47** 198–209

Prakash P V, Rao S R and Parija S C 2005 Emergence of unusual species of enterococci causing infections, South India; *BMC Infect. Dis*. **5** 14 (Accessed at: *http://www.biomedcentral.com/1471-2334/5/14*)

Prashant K and Badrinath S 2004 *In vitro* susceptibility pattern of *Actinctobacter* species to commonly use cephalosoporins, quinolones and aminoglycosides; *Indian J. Med. Microbiol*. **22** 97–103

Raghunath D and Kher S K 1989 Antibiotic therapy of Salmonellosis. Editorial; *Med.. J. Armed Forces India* **45** 3–4

Ramachandran R and Narayanan P R 2008 Current status of drug resistance of tuberculosis in India; in *Proceedings of the 9th Sir Dorabji Tata Symposium* March 10-11, 2008 (in press)

Rappuoli R and Coracci A 2003 Reverse vaccinology and genomics; *Science* 2003 **302** 602

Ray K, Bala M, Gupta S M, Khunger N, Puri P, Muralidhar S and Kumar J 2006 Changing trends in sexually transmitted infections at a Regional STD Centre in north India; *Indian J. Med. Res*. **124** 559–568

Reed S D, Lakshminarayan R, Black D J and Sullivars S D 2002 Economic issues and antibiotic resistance in the community; *Ann Pharm*. **36** 148–154

Rice L B 2008 The Maxwell Finland Lecture: For the Duration-Rational Antibiotic Administration in an Era of Antimicrobial Resistance and *Clostridium difficile*; *Clin. Infect. Dis*. **46** 491–496

Rodrigues C 2008 XDR TB – a global perspective and in a tertiary Indian hospital with special focus on drug Susceptibility Testing (DST); in *Proceedings of the 9th Sir Dorabji Tata Symposium* March 10-11, 2008 (in press)

Rodrigues C, Joshi P, Jani S H, Alphonse M, Radhakrishnan R and Mehta A 2004 Detection of *β*lactamases in Nosocomial gram negative isolates; *Indian J. Med. Microbiol.* **22** 247–250

Saha D, Karim M M, Khan W A, Ahmed S, Salam M A and Bennish M L 2006. Single-dose azithromycin for the treatment of cholera in adults; *New Engl. J. Med*. **354** 2452–2462

Scollard D M, Adams L R, Gillis T P, Krahenbubl J L, Truman R W, Williams D L 2006 The continuing challenges of Leprosy; *Clin. Microbiol. Rev*. **19** 338–381

Sen B, Dutta S, Sur D, Manna B, Dev A K, Bhattacharya S K and Niyogi S K 2007 Phage typing, biotyping and anti-microbial resistance profile of *Salmonella enterica* sero-type *Typhi* from Kolkata; *Indian J. Med. Res*. **125** 685–688

Seppala H, Klankka T, Vupio-Varkila J, Muotiala A, Helenins H, Lager K, Huovinen P 1997 Finnish Study Group for Antimicrobial Resistance. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A Streptococci in Finland; *N. Engl. J. Med*. **337** 441–446

Sharma N C, Mandal P K, Dhillon R and Jain M 2007 Changing profile of *Vibrio cholerae* 01, 0139 in Delhi and periphery (2003–2005); *Indian J. Med. Res*. **125** 633–640

Shukla I, Tiwari R and Agarwal M 2004 Prevalence of Extended Spectrum *β* lactamase producing *Klebsiella pneumoniae* in a tertiary care hospital; *Indian J. Med. Microbiol*. **22** 87–91

Singhal R, Dhawan S, Mohanty S, Sood S, Dhawan B, Das B and Kapil A 2006 species distribution and antimicrobial susceptibility of coagulase negatice staphylococci in a tertiary care hospital; *Indian J. Med. Res*. **123** 569–570

Singhal S, Purnapatre K P, Kalia V *et al* 2007. Ciproploxacin-resistant *Neisseria meningitides*, Delhi, India; *Emerg. Infect. Dis*. **13** 1614–1616

Sinha M and Srinivasa H 2007 Mechanisms of Resistance to Carbapenems in Meropenem resistant *Acinetobacter* isolates from clinical samples; *Indian J. Med. Microbiol*. **25** 121–125

Stewart W H 1967 A mandate for state action. in *Proceeding of the Association of State and Territorial Health Officer* (*http://pages.pomona.edu/˜nvh04747/Bio189L/intro.html*)

Streulens M .J 2003 The problem of resistance; in *Antibiotic and chemotherapy* Chapter 3, 8th edition (eds) R G Finch, D

Greenwood, S R Norrby, and R J Whitley (Edinburgh: Churchill Livingstone) pp 25–47

Ultley A H C, Collins C H, Naidoo J and George R C 1988 Vancomycin-resistant Enterococci; *Lancet* **1** 57–58

U S Food and Drug Administration, Centre for DrugEvaluation and Research 2007 *New molecular ntities (NMEs)* (*http://www.fda.gov.cder/rdmt/*)

Venugopal D, Kumar S, Isa M and Bose M 2007 Drug Registance profile of Human *Mycobacterium avium* complex strains from India; *Indian J. Med. Microbiol.* **23** 115–120

Wattal C 2008 *Sir Ganga Ram Hospital, Microbiology Newsletters* May 2000 to Oct 2005 (URL *http://www.sgrh.com/nletter/n1.htm*) 4th June 2006) also accessed on 24th May 2008.

Whitney C G and Klugman K P 2004. Vaccines as tools against resistance: the example of phenomococcal conjugate vaccine period; *Semin. Pediactr. Infect. Dis.* **15** 86–93

Wilson G, Easow J M, Mukhopadhyay C and Shivananda P G 2006 Isolation and antimicrobial susceptibility of *Shigella* from patients with acute gastroenteritis in Western Nepal; *Indian J. Med. Res.* **123** 145–150

Wise R, Hart T, Cars O, Struelens M, Helmith R, Hnovinen P and Sprenger M 1998 Resistance is a major threat to public health; *Br. Med. J.* **317** 609–610

Wise R 2008 The world-wide threat of Resistance? (Keynote address); in *Proccedings of the 9th Sir Dorabji Tata Symposium* 10-11, March 2008 (in press)

World Health Organization 2002 Fact Sheet No. 194 Antimicrobial Resistance; available at *http://www.who.int/mediacentre/factsheets/FS194/en/print.html.* Accessed on 6th May 2008

World Health Report 2003 *Shaping the future* (Geneva, World Health Organization) (*URL: http//www.who.int/war/2003/eu/)*

World Health Report 2007 *A safer future* (Geneva: World Health Organization) (URL: *http://www.who.int/whr/2003/en/*)

Yavankar S P, Pardesi K R and Chopade B A 2007 Species distribution and Physiological characterization of *Acinetobacter* Genospecies from Healthy Human Skin of Tribal population in India; *Iindian J. Med. Microbiol*. **25** 336–345