OXOID™

culture

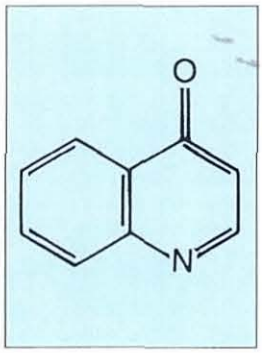
Volume 13 No 2
September 1992
ISSN 0965-0989

Neisseria meningitidis **diplococci which cause pharyngitis and meningitis.**
Courtesy of Bayer AG from their publication *ARS Bacteriologica* (artist: Carl W Röhrig).

The quinolones—an expanding class of antibiotics

Laura JV Piddock,
Antimicrobial Agents
Research Group,
Department of Infection,
University of Birmingham, UK

Review of the bacteriology and mechanisms of action of this rapidly expanding class of oral antimicrobial agents.



Emporiatics and jet flights

Robert G Masterton,
Consultant,
Western General Hospital,
Crewe Road,
Edinburgh EH4 2XU, UK

How the increasing use of international air transport is leading to widespread travel-related illness.

The quinolones—an expanding class of antibiotics

Laura JV Piddock, PhD, Antimicrobial Agents Research Group, Department of Infection, University of Birmingham, UK.

Introduction

Quinolones are a rapidly expanding class of oral antimicrobial agents, ranging from the early non-fluorinated analogue, nalidixic acid with a narrow spectrum of activity, to broad-spectrum fluorinated agents such as ciprofloxacin. Many compounds have been developed with additional substituents on the basic 4-quinolone nucleus (**Figure 1**), but the addition of a fluorine at position 6 has greatly enhanced the antibacterial activity and pharmacokinetics of these agents in man. The early agents were active only against Gram-negative pathogens and achieved very low concentrations in serum; consequently, these agents were used only in the treatment of urinary tract infections. The fluorinated quinolones are active against Gram-negative and Gram-positive bacteria, and recently agents such as tosufloxacin have been synthesised that are active against anaerobic bacteria (**Table 1**). All fluorinated quinolones have vastly improved pharmacokinetics compared with those of the early agents nalidixic and oxolinic acid. Substitutions on the 4-quinolone nucleus have further altered these properties. Some agents (e.g. lomefloxacin) have extremely long half-lives so that instead of the usual dosing of three times daily, once-a-day oral therapy is possible. Most quinolones are also available as intravenous formulations.

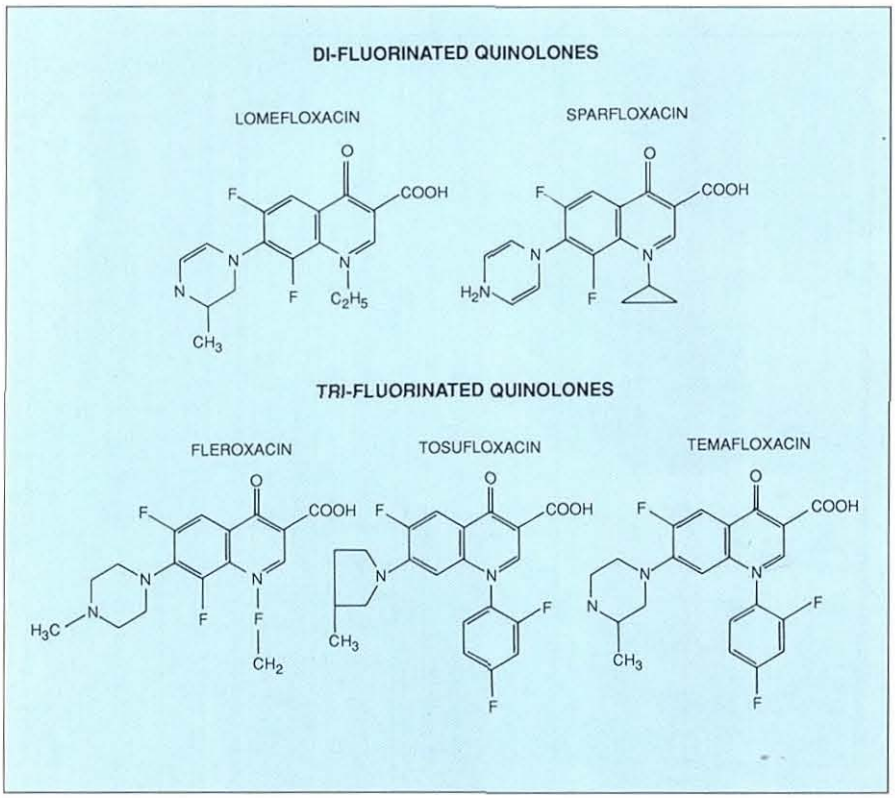


Figure 1: Examples of typical quinolones.

Mechanism of action

The primary mechanism of action of quinolones is by inhibition of bacterial DNA gyrase, an essential intracellular enzyme involved in maintaining the topology of the chromosome within the cell.[1] In *Escherichia coli*, DNA gyrase is made up of two A-subunits encoded by the *gyrA* gene, and two B subunits encoded by the *gyrB* gene. The tetrameric enzyme catalyses several functions including the supercoiling of DNA, an event involving the breakage and reunion of double-stranded DNA. The exact bactericidal mechanism of action of the quinolones has yet to be determined. It has been proposed that the initial event is the inhibition of DNA synthesis[2,3] through interference with the DNA nick-sealing activity of DNA gyrase.[4–6] An alternative model has been proposed by Shen and Pernet[7] for the interaction of quinolones with DNA or a DNA gyrase–DNA complex.[8,9] However, this model has not been supported by other workers.[10] It has also been shown that the concentration of quinolones required to inhibit DNA supercoiling, or other enzymatic reactions catalysed by DNA gyrase (e.g. cleavage and linkage reactions), is higher than the MIC (minimum inhibitory concentration) of the same agent for the same bacterial strain from which the DNA gyrase was purified. However, DNA gyrase is

Table 1: Typical susceptibility of wild-type bacteria to quinolones at 10^6 colony-forming units per ml.

	Non-fluorinated	Mono-fluorinated							Di-fluorinated		Tri-fluorinated		
Species	NAL	CIP	NOR	ENX	AMI	OFX	PEF	RUF	LOM	SPA	TOS	FLX	TEM
Escherichia coli NCTC 10418	4	0.015	0.06	0.06	0.06	0.06	0.12	0.5	0.12	0.03	0.03	0.12	0.25
Pseudomonas aeruginosa NCTC 10662	128	0.25	1	2	1	2	2	16	4	1	0.5	2	4
Staphylococcus aureus NCTC 8532	64	0.5	2	2	2	0.5	0.5	2	1	0.06	0.12	2	1
Bacteroides fragilis NCTC 9343	>128	16	64	128	–	8	–	–	–	2	1	–	4

NAL, nalidixic acid; CIP, ciprofloxacin; NOR, norfloxacin; ENX, enoxacin; AMI, amifloxacin; OFX, ofloxacin; PEF, pefloxacin; RUF, rufloxacin; LOM, lomefloxacin; SPA, sparfloxacin; TOS, tosufloxacin; FLX, fleroxacin; TEM, temafloxacin.

clearly the target of the quinolones as mutations in *gyrA* confer bacterial resistance and the concentration of quinolone required to inhibit the reactions of DNA gyrase from the resistant organism increases by the same order of magnitude as the MIC of the drug. Kreuzer and Cozzarelli[11] suggested that the binding of quinolone to DNA gyrase may cause it to act as a 'cellular poison'; therefore very low concentrations are required to exert a bactericidal effect. It was suggested that nalidixic acid binds to DNA gyrase and DNA, thereby trapping an enzyme intermediate at the replication fork thus inhibiting the unwinding of the DNA duplex and hence DNA replication.[12] Recent evidence (ref. 9 and A Maxwell, personal communication) suggests that quinolones interact with a DNA gyrase–DNA complex and not to the enzyme or DNA alone, providing further support for the poison hypothesis.

There is excellent correlation between the MIC and the concentration of quinolone required to inhibit DNA synthesis in *E.coli* and other bacteria by 50%.[2,3] It has been observed that inhibition of protein synthesis (e.g. by chloramphenicol) decreases the bactericidal activity of quinolones.[13] High concentrations of quinolones can also inhibit protein and RNA synthesis, resulting in a paradoxical response: below a certain concentration there is a progressive increase in bactericidal action up to the 'optimum bactericidal concentration' (OBC) above which there is a decrease in bactericidal activity due to inhibition of protein and RNA synthesis. It has also been shown that quinolones induce the DNA repair (SOS) response,[14] a consequence of which is the inhibition of cell division. Inhibition of protein synthesis also inhibits induction of RecA (a primary enzyme in the SOS response) and maximum induction of RecA is seen at the

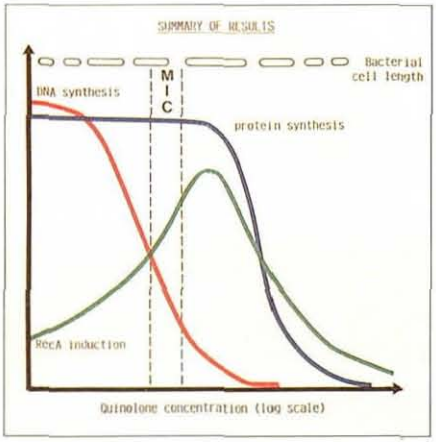


Figure 2 : Experimental results.

OBC (**Figure 2**); but inhibition of protein synthesis by chloramphenicol has no effect on the inhibition of DNA synthesis by quinolones.[3,11] Therefore, it has been proposed that the primary event in the bactericidal action of quinolones is the inhibition of DNA synthesis due to the interaction of quinolones with DNA gyrase, and that induction of the SOS response, and therefore inhibition of cell division, is consequential but also bactericidal.[3]

Accumulation of quinolones in bacteria

The ability of quinolones to permeate bacteria to reach their intracellular target is an important factor in determining both the spectrum of organisms affected and the activity of the compounds; reducing penetration can decrease bacterial susceptibility to these drugs. Quinolones have several permeability barriers to overcome in order to obtain access to their target site.[15] In Gram-negative bacteria both the outer membrane and the cytoplasmic membrane have to be traversed, whereas in Gram-positive bacteria, essentially only one membrane has to be crossed. A definitive model for the mechanism of quinolone accumulation is not available; however, the process by which the final intracellular concentration of quinolone is achieved is complicated. Most research has been with *E.coli* (although other bacteria have been studied) and on norfloxacin or ciprofloxacin. Regardless of the species or quinolone studied, all strains show rapid accumulation, reaching a plateau or steady-state within minutes. Using 10µg/ml quinolone (27–45µM depending on the agent), a steady-state is usually reached between 60 and 180 seconds with steady-state between 50 and 150ng quinolone per mg dry cells[16,17] (**Figure 2**). Accumulation is apparently non-saturable, but not many quinolones have been studied. No competitive accumulation between enoxacin or ciprofloxacin has been observed.[18] Using mutants of Gram-negative bacteria lacking certain outer membrane proteins (Omps), some quinolones have been shown to penetrate the outer membrane *via* the pore-forming proteins (porins)—primarily OmpF—which has been confirmed by the isolation of quinolone-resistant mutants that lack OmpF which were 2–4-fold less susceptible to all quinolones.[19–21] The passage of quinolones through the outer membrane does not appear to be limited to the porins—other routes of penetration have also been suggested.[22] Magnesium ions decrease the activity and accumulation of quinolones, either due to the formation of complexes which are then too bulky to diffuse through OmpF, or due to the cations stabilising the outer membrane by chelating with lipopolysaccharide (LPS), thus preventing damage by the quinolones that would promote their own accumulation.[21] Self-promoted accumulation has previously been shown for other antimicrobial agents such as aminoglycosides.[23] Studies using strains with mutations affecting LPS (e.g. *S. typhimurium rfa*) showed that the susceptibility to older agents (non-fluorinated) such as nalidixic acid or oxolinic acid is decreased, whereas new agents (fluorinated) were affected.[18] The contribution of the porin and non-porin pathways to total accumulation of a given quinolone is dependent upon the hydrophobicity of the drug; the more hydrophilic the drug, the less able it is to penetrate the phospholipid bilayer of the bacterium. Reduced temperature decreases quinolone accumulation, which may suggest a catalytic process is involved. Acid pH also decreases accumulation, possibly due to an alteration of the overall electrical charge of fluoroquinolone. Quinolones usually have two pK_a, one at approximately pH 6 (a carboxylic acid group) and the other at approximately pH 8.8 (an amino group). As the pH changes from alkali to acid the molecule becomes protonated at these groups, thereby altering the overall charge. At neutral pH most quinolones will exist in two forms, with approx. 90% in zwitterionic form and 10% as undissociated acid. The data would suggest that the overall penetration pathway preferentially allows accumulation of the zwitterion. Therefore, as the pH decreases from neutrality, less of the zwitterion is available and so there is less accumulation. Alternatively, the pH may be having another effect; a decrease in external pH can cause a decrease in the transmembrane electrical potential, suggesting that accumulation across the cytoplasmic membrane may be coupled to the proton motive force (p.m.f.).

There is good evidence that there is an energy-dependent quinolone efflux system which is energised by the p.m.f. operating in the cytoplasmic membrane, possibly involving a carrier protein. Biochemical data suggest efflux of quinolones from Gram-negative bacteria,[24] but for *S.aureus* the gene *norA* has been identified.[25] The amino acid sequence of NorA suggests that the protein has some homology with proteins involved in the efflux of other molecules from bacteria and it has several regions that span the cytoplasmic membrane.

Mechanisms of resistance to quinolones

Unlike other classes of antimicrobial agents, no enzymatic mechanisms of resistance have been described to date, and there is only one proven case of plasmid-mediated resistance.[26] Mutations in several chromosomal genes of *E.coli* affect quinolone activity but there are essentially only two classes of resistance.

The first class includes all the mutations at *gyrA*, and some at *gyrB*, which encode a DNA gyrase with decreased susceptibility to quinolones; the second class includes those mutations that cause a decrease in the amount of quinolone accumulated. Much work has been performed on sequencing quinolone-resistant *gyrA*, and although several mutations have been identified all affect the part of the protein located near to tyrosine-122 in GyrA.[28–31] The substitution of different amino acids caused by the different nucleotide substitutions (mutation) in *gyrA* confer a different degree of resistance (10–100-fold increase in the MIC of quinolones). The substitution of serine-83 by tryptophan occurs most frequently in the laboratory and in clinical isolates, and confers the highest increase in the MIC of the quinolone. The amino acid sequence of GyrA is very similar in different bacterial species and interestingly it has been shown that in quinolone-resistant *S.aureus* the mutation in *gyrA* confers an amino acid substitution at serine-84 and/or serine-85.[32] Mutations substituting amino acids at both serine molecules are additive, thereby giving the highest increase in the MIC of quinolones. Quinolone-resistant bacteria of other species are biochemically similar to the *gyrA* mutants of *E.coli*; however, no molecular biological study has yet been made. Mutations in *E.coli gyrB* conferring altered susceptibility to quinolones have also been identified,[33] and it has been proposed that they alter the net electrical charge associated with DNA gyrase so that it repels or attracts the drug.

The second class of resistance includes the mutations that affect the accumulation of

quinolones. Essentially, these fall into two groups—those that decrease the accumulation of quinolones and those that increase the efflux of quinolones. Mutations in *E.coli ompF* or the regulatory locus for OmpF, *ompR*, decrease the accumulation of most quinolones and increase the MIC of most agents 4–16-fold. In addition, *marA* (which encodes an antisense RNA which decreases the production of OmpF) has a lower initial rate of accumulation and steady-state concentration of norfloxacin than *E.coli ompF*$^-$, suggesting that *marA* regulates another factor associated with accumulation.[24] Mutations affecting LPS have also been shown to confer quinolone resistance and decreased accumulation.[19] Enhanced efflux of quinolones as a mechanism of resistance has been shown in *S.aureus*[26] and *Proteus vulgaris*.[27] In *S.aureus*, resistance was mediated by *norA* encoded on a plasmid; this is the first report of transferrable quinolone resistance.

At present the majority of quinolone-resistant clinical isolates have mutations in *gyrA*, and the MICs of quinolones are usually 100-fold higher than the MIC_{50} for typical susceptible strains for each species. Therefore, the MICs of the less active quinolones against resistant mutants are more likely to be above the recommended breakpoint concentrations, which are usually between 1 and 4μg/ml. For example, *Pseudomonas aeruginosa* is inherently less susceptible to quinolones than members of the Enterobacteriaceae, so the MIC_{50} for this species is much higher than that for *E.coli*. A strain of *E.coli* with a mutation in *gyrA* may still be inhibited by the breakpoint concentration of ciprofloxacin (1μg/ml), whereas a strain of *P.aeruginosa* with a mutation in *gyrA* is unlikely to be inhibited by this concentration, because its MIC against ciprofloxacin will be 2–8μg/ml. Therefore, it is not surprising that quinolone-resistant clinical isolates usually arise in species that are inherently less susceptible to quinolones, and/or in patients with abnormal pharmacokinetics giving rise to lower than expected tissue and body fluid concentrations. Recently, highly quinolone-resistant clinical isolates of Enterobacteriaceae have been described with the resistance attributed to several mutations affecting more than one mechanism.[27] In many instances quinolone-resistant bacteria are only cross-resistant to other quinolones and can be eradicated by using an alternative antimicrobial agent of another class. However, mutants with decreased accumulation of quinolones are often cross-resistant to other agents of different antibiotic classes which use common pathways. Therefore, if these mutants arise during therapy an alternative drug may not be available; to date these mutants are extremely rare outside the laboratory. It has been suggested that quinolone-resistant mutants are at a physiological disadvantage compared with wild-type susceptible bacteria; however, while bacteria with certain mutations grow more slowly in the laboratory or can be shown to lack the ability to produce certain markers of pathogenicity, resistant bacteria have and will continue to arise during quinolone therapy, some causing clinical failure. The incidence of quinolone resistance in the UK is approximately 1%, although this value will vary for different species and by region. In summary, despite increased usage of these agents over recent years there has not been a marked increase in the number of resistant isolates.

The future

Fluorinated quinolones are continuing to be synthesised with the aim of extending their spectrum of activity and improving their pharmacokinetics. Alterations in specific properties of quinolones, resulting from changing the substituents on the 4-quinolone core molecule, means that certain agents will be more useful for treating certain infections: e.g. temafloxacin and respiratory tract infections, or lomefloxacin and sexually transmitted diseases. Resistant bacteria will continue to be isolated and some will cause therapy to fail; unfortunately, as with other antimicrobial agents, it is unlikely that there will be a quinolone in the near future that does not have this problem.

References

1. Reece, R.J. and Maxwell, A. (1991). *Crit. Rev. Biochem. Mol. Biol.*, **26:** 335–375.
2. Chow, R.T. *et al.* (1988). *Antimicrob. Agents Chemother.*, **32:** 1113–1118.
3. Piddock, L.J.V. *et al.* (1990). *Antimicrob. Agents Chemother.*, **34:** 2331–2334.
4. Gellert M. *et al.* (1977). *Proc. Natl. Acad. Sci. USA*, **74:** 4772–4776.
5. Higgins, N.P. *et al.* (1978). *Proc. Natl. Acad. Sci. USA*, **75:** 1773–1777.
6. Peebles, C.L. *et al.* (1978). *Cold Spring Harb. Symp. Quant. Biol.*, **43:** 41–52.
7. Shen, L.L. and Pernet, A.G. (1985). *Proc. Natl. Acad. Sci. USA*, **82:** 307–311.
8. Shen, L.L. *et al.* (1989). *Biochemistry*, **28:** 3886–3894.
9. Shen, L.L. *et al.* (1989). *J. Biol. Chem.*, **264:** 2973–2978.
10. Palu, G. *et al.* (1988). *Biochem. Pharmacol.*, **37:** 1887–1888.
11. Kreuzer, K.N. and Cozzarelli, N.R. (1980). *Cell*, **20:** 245–254.
12. Drlica, K. *et al.* (1980). *Proc. Natl. Acad. Sci. USA*, **77:** 6879–6883.
13. Smith, J.T. (1984). *Pharm. J.*, **15:** 299–305.
14. Piddock, L.J.V. and Wise, R. (1987). *FEMS Microbiol. Lett.*, **41:** 289–294.
15. Piddock, L.J.V. (1991). *J. Antimicrob. Chemother.*, **27:** 399–405.
16. Mortimer, P.G.S. and Piddock, L.J.V. (1991). *J. Antimicrob. Chemother.*, **28:** 639–654.
17. Asuquo, A. and Piddock, L.J.V. (1992). Killing kinetics and accumulation of fourteen quinolones into *E.coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Submitted for publication.
18. Bedard, J. *et al.* (1987). *Antimicrobial. Agents Chemother.*, **31:** 1348–1354.
19. Hirai, K. *et al.* (1986). *Antimicrob. Agents Chemother.*, **29:** 535–538.
20. Hirai, K. *et al.* (1986). *Antimicrob. Agents Chemother.*, **30:** 248–253.
21. Chapman, J.S. and Georgopapadakou, N.H. (1988). *Antimicrob. Agents Chemother.*, **32:** 438–442.
22. Hooper, D.C. *et al.* (1989). *Antimicrob. Agents Chemother.*, **33:** 283–290.
23. Hancock, R.F.W. *et al.* (1981). *Antimicrob. Agents Chemother.*, **19:** 777–785.
24. Cohen, S.P. *et al.* (1988). *Antimicrob. Agents Chemother.*, **32:** 1187–1191.
25. Yoshida, H. *et al.* (1990). *J. Bacteriol.* **172:** 6942–6949.
26. Tanaka, M. *et al.* (1991). Characterisation of high-level quinolone resistance in methicillin-resistant *Staphylococcus aureus*. *Proceedings of the 31st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago*, Abstract 808.
27. Ishii, H. *et al.* (1991). *J. Antimicrob. Chemother.*, **28:** 827–836.
28. Yoshida, H. *et al.* (1988). *Mol. Gen. Genet.*, **211:** 1–7.
29. Cullen, M.E. *et al.* (1989). *Antimicrob. Agents Chemother.*, **33:** 886–894.
30. Oram, M. and Fisher, L.M. (1991). *Antimicrob. Agents Chemother.*, **35:** 387–389.
31. Hallett, P. and Maxwell, A. (1991). *Antimicrob. Agents Chemother.*, **35:** 335–340.
32. Sreedharen, S. *et al.* (1991). *Antimicrob. Agents Chemother.*, **35:** 2151–2154.
33. Yamagishi, J. *et al.* (1986). *Mol. Gen. Genet.*, **204:** 367–373.

Emporiatrics and jet flights

Robert G Masterton, Consultant, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK.

Introduction

Emporiatrics is more widely recognised in the United States than the United Kingdom and is the name given to the specialty concerned with the health of travellers. Paradoxically, given that it arose from the health care problems surrounding jet travel, emporiatrics is derived from the Greek 'emporos', meaning 'shipboard passenger'. However this derivasion is true to its origin which lies in the 40 day detention period (Italian 'quaranta' = 40; leading to 'quarantine') applied in Marseilles in 1383 to all travellers from infected ships, as prevention against outbreaks of bubonic plague.

Journeys that involved handfuls of travellers on sailing ships taking many months are now completed in hours by aircraft (such as the Boeing 747) which can carry some 400 people non-stop up to 6,500 miles. The World Tourism Organisation has estimated over 1,000 million arrivals in the UK per annum, the largest expansion being in air travel which increased 31-fold from 1949 to 1986 and now accounts for some two-thirds of all trips abroad.[1] It is not just the volume of travel which has highlighted international problems related to the transport of diseases. There is now much greater freedom to cross the globe and do so for a wide variety of reasons: businessmen, tourists, sportsmen, students, the military, refugees, emigrants or immigrants returning to their original home to visit family and friends. The durations of stay and living conditions whilst abroad also vary and expose the different travelling groups[2] to a multitude of different health care problems (**Table 1**) which can become apparent whilst abroad or after returning home.

The spectrum of diseases

Travel-related illnesses are invariably perceived as afflicting visitors from civilised countries who fall victim to exotic diseases in less developed areas of the world

Figure 1: 19th century victims of yellow fever buried on Ascension Island who died after returning from journeys to the UK, having acquired the disease elsewhere.

(**Figure 1**). This is a misconception. Some infections, e.g. cytomegalovirus, are common world-wide and can affect the susceptible host whether at home or abroad. In others, 'exotic' infections such as Legionellosis and fungal meningitis may result from travel to developed countries, e.g. Europe and North America. As a recent French study of kala-azar demonstrated, a disease commonly viewed as tropical may be mainly local with only a minority of cases (20%) related to travel.[4]

The consequences of transported human pathogens may be insidious and delayed. Diseases such as tuberculosis and strongyloides infestation can present themselves many years after exposure. The full significance of an imported organism may not lie in the individual case but in the ability of that strain to spread within its new domicile, e.g. methicillin-resistant *Staphylococcus aureus* from Australia. Similarly the introduction of organism variants with novel antibiotic resistance patterns can compromise a nation's current prescribing habits, e.g. penicillin resistance in beta-lactamase positive *Neisseria gonorrhoeae* from Africa and the Far East. Even when considering the individual traveller, the problems are often commonplace with gastrointestinal and respiratory conditions predominating and non-infectious illnesses, e.g. psychiatric disturbances and menstrual disorders, forming a significant proportion of travel-related health problems (**Table 2**).[2,5]

Although the grim epidemics of the Middle Ages no longer flourish, travel is still important in the dissemination of diseases such as meningococcal meningitis from the Haj and the inexorable spread of the human immunodeficiency virus.[1]

Aircraft-related diseases

Despite a recent article suggesting that air-flight staff may be at greater risk of *Entamoeba histolytica* infections,[6] there is little evidence that airline travel presents an occupational infection hazard. For example, Swissair found no increased incidence over national norms of hepatitis A or B infections in its flight personnel.[1]

With the exception of gastroenteritis and malaria there is also little in the literature to give cause for concern to passengers. However, both staff and passengers are vulnerable when infection invades the aircraft, whether by a vehicle such as food, or by an infected traveller or insect vector. Sharing headsets may cause otitis externa and an outbreak of influenza A involving 36 passengers and two crew members once occurred following exposure to the primary case, a passenger, when a ground delay was compounded by an inoperative ventilation system.[1]

Table 1: Incidence of illness in different types of short-term travel.[3]

	Beach Holiday (%)	Group Tour (%)	Individual Tour (%)	Adventure Holiday (%)
Experienced a health problem	73	77	75	78
Any illness	20	20	23	27*
Confined to bed	5	3	5	8*
Fever	4	3	4	6*
Diarrhoea	31	34	35	37

* Chi squared test Adventure compared to other types $p<0.001$

Table 2: Health problems in different types of traveller (% reporting).

	Long-stay India[5]	Holidaymaker Europe/Mediterranean[2]
None	N/A	63
Alimentary	71	28
Respiratory	63	3
Skin	39	N/A
Menstrual disturbance*	28*	N/A
Others	24	3

* = percentage of females surveyed.

Table 3: Large outbreaks of foodborne illness associated with airline meals.

Year	Food source	Number affected (passenger/aircrew)	Food	Organism
1973	Portugal	247/0	Custard	*Staph.aureus*
1975	Alaska	196/1	Ham in omelette	*Staph.aureus*
1976	Spain	550/N/A	Egg salad	*S.typhimurium*
1976	France	232/58	Cold dishes	*S.brandenberg*
1984	Britain	631/135	Aspic	*S.enteritidis*

Gastroenteritis

Whilst it is likely that gastroenteritis related to airline catering frequently goes unreported, since 1961 there have been at least 30 major outbreaks relating to commercial aircraft.[1,7,8] Five of these involved over 100 passengers (**Table 3**) and in nine outbreaks, aircrew illness was reported. Even these figures hide the true potential magnitude of the problem—in one outbreak it was calculated that 220,553 passengers had been 'at risk'![8] A wide range of organisms comprising *Salmonella* (both *typhi* and non-*typhi*), *Staphylococcus aureus*, *Clostridium perfringens*, *Vibrio cholerae* (both 01 and non-01), *Shigella* and *Vibrio parahaemolyticus* have caused these episodes, which to date have all been foodborne. Usually illness has declared itself after arrival but in the modern, longer-duration flights or in toxin-related cases, symptoms may start in the air. Those investigations which have been undertaken have shown food-handling errors to be most commonly implicated, frequently with inappropriate holding temperatures either during or after meal preparation. As late as 1984, 20% of American flights were holding food at too high a temperature.[1] Although aviation catering guidelines do now exist and considerable efforts are made to meet these standards, problems with refrigeration still occur.

Food handlers, either whilst symptomatic or as carriers, are less frequently involved and have only played an important role in three outbreaks (*S.enteritidis*, *S.typhi* and *S.aureus*).[8,9]

Such episodes of gastroenteritis are no respecter of status or country—one of the biggest outbreaks was initially reported by first class transatlantic Concorde passengers[8]—and they directly impute poor flight catering practices. Whilst bacterial contamination of food is commoner in developing countries,[10] there is no cause for complacency elsewhere. In a 1984–6 UK airline meal survey, 24% of samples showed high surface colony counts indicating unsatisfactory bacterial contamination and 0.4% yielded *Salmonella* spp.[7] To date all outbreaks would appear to have been preventable by proper cooking, effective temperature control and correct food handling. It is therefore depressing and a sad comment on our abilities to learn from the past that these episodes should continue to occur.

In relation to the very large number of meals served on aircraft (over 50 million meal units per annum from Heathrow Airport, London alone), incidents of food poisoning are rare. However, they are the largest reported cause of passenger illness and the commonest cause of in-flight crew incapacitation.[11] They can also cause death and have even led to international disputes at government level, e.g. the commercial retaliation this year between Peru and Argentina related to the cholera outbreak, which involved a Boeing 747 flying from South America to California.[12]

Malaria (Figure 2)

Despite the inter-relationship between travel and malaria being well recognised and the availability of drug and physical prophylaxis, there are approximately 2,000 malaria cases per annum in the UK with a fatality rate of 0.36%.[13] Although the danger of misleading epidemiological data has been highlighted,[14] the risk of malaria in British residents returning from endemic areas relates to the travel zone visited (Oceania being the greatest risk); increasing duration of stay; purpose of travel (business travellers have the highest attack rates in East Africa), and chemoprophylaxis.[15] This latter aspect reflects the failure to seek or comply with therapy plus suboptimal drug selection, which even in the best circumstances is only 73% effective against *Plasmodium falciparum* in some countries.

Although contributing only a very small amount to the total number of cases, much interest surrounds the curiosity of 'airport malaria', which manifests itself in a variety of forms each involving stowaway mosquitoes:[1]

1. Primary flight associated—travellers are bitten during a flight from a malarious area to a non-malarious area.
2. Secondary flight associated—malaria develops in a traveller following a flight between two non-malarious countries but in an aircraft from an endemic area.
3. Runway malaria—malaria follows a flight from one non-endemic area to another where exposure to the vector occurs when the aircraft doors are opened during a short runway stopover in a malarious country.
4. 'Classical' airport malaria—malaria occurs in residents living near an airport in a non-malarious country. Infection is not related to travel at all but to a mosquito disembarking from an aircraft returned from an endemic zone.
5. Baggage malaria—on this occasion malaria occurs in a person living in a non-endemic country and outside mosquito flight range from an airport (12km). Exposure is thought to arise from insects packed in luggage and released once the traveller from a malarious area has arrived home.

It can readily be appreciated that diagnosis in these circumstances, where there is frequently no history of travel at all, let alone to a malarious zone, is very difficult. One can only marvel at the clinical acumen of the Italian doctor who diagnosed falciparum malaria in two Swiss travellers to his

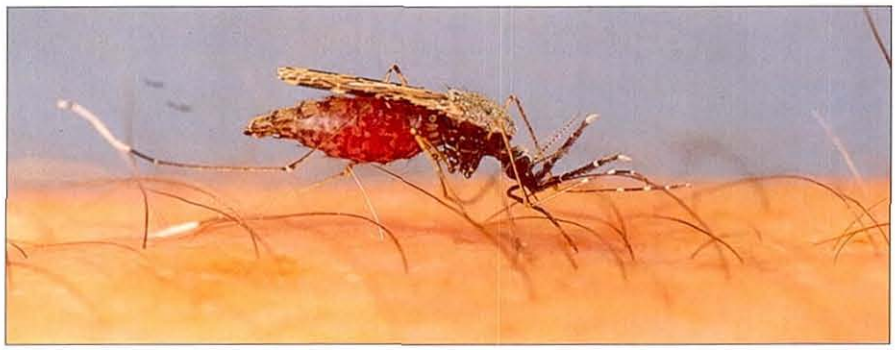


Figure 2: South American species of malarial mosquito (*Anopheles albimanus*) feeding from human arm.

country. The father and son had not been abroad for 25 years but lived 3km from the international airport at Geneva![16]

Travelling insects

It is not just humans who travel in aircraft but all manner of life forms, which can result in a wide variety of flight hazards, e.g. rodents such as the black rat which grounded a Boeing 747.[17] Insects, including mosquitoes, are included in this list and their importance to passengers as disease vectors has already been described. However, of more general and major concern is the potential this form of 'hitch-hiking' infected vector has for disease transmission to, and subsequent establishment within, non-endemic countries, e.g. arbo viruses, including yellow fever.

Insects can travel either in or on aircraft. On the older, slower, propeller-driven aeroplanes, a wide variety of insects were shown to survive on the outside skin.[1] In modern jets mosquitoes can survive flights of 6–9 hours in the wheel bays and a survey looking at insect transmission between countries found 18% of flights from tropical countries carried live insects.[18]

Despite this very real danger, no major international health problem has been reported due to insect travel on aircraft. However, prevention is crucial and although all airports are supposed to ensure a vector-free zone around and within their precincts, this is of doubtful efficiency in some countries. The other preventative weapon is insect control with work continuing in this field to ensure the effective killing of insects throughout the aircraft. The current recommendation is for cabin insect control to occur at 'top of descent' but strict adherence to proper distribution of the correct volume of insecticide is essential and in the past insufficient attention to this has resulted in proven insecticide failures.

Better to travel carefully...

History is littered with anecdotes and experiences of travel-related illnesses. Shakespeare recognised the value of preventative measures with a warning about sexually transmitted diseases—"Those girls of Italy, take heed of them."—in 'All's Well That Ends Well". In 1899 a well known hazard for missionaries to Africa was 'danger at the hands of inexperienced medical officers'—little has changed (see below). A large number of articles exist which document and quantify the health problems which arise from travel and now this is being met by an almost equal volume of papers dealing with travel health care precautions.[1] It was calculated that in 1986, 12% of UK travellers (2.15 million people) suffered illness with a cost to the country of about £10 million.[2]

Table 4: Pre-travel history.

The traveller	— personal details
	— medical history including GP's details
	— current medication
	— allergies
	— immunisation history
The travel	— nature of travel
	— dates and duration of travel
	— countries to be visited
	— medical arrangements including local services and insurance cover

Against this background, the general ignorance that persists about travel health care is both surprising and disappointing. Until recently, commercial travel firms have put little serious effort into advising their clients of health hazards and how to prevent them. Surveys of travellers have shown a lack of awareness and failure to respond to advice.[1] The medical profession, which tends to concentrate almost exclusively on therapeutic, as opposed to lifestyle preventative measures, has demonstrated widespread inadequate knowledge leading to inefficient and inappropriate immunisation and chemoprophylaxis advice.[1] Nor have the health services responded well to the issue, with only recently one London authority still refusing to view advice on foreign travel as health promotion.[17]

However, improvements are evident with travel advice clinics arising in commercial settings, specialist tropical medicine centres and some health authorities. Recognition is also growing in community care with an appreciation of the full range of preventative measures available. It is impossible to stop all travel-related illness but problems can be avoided by taking sensible and appropriate steps. The key to this, as to most medicine, lies first in taking a full history (**Table 4**) against which can be set advice covering personal and environmental risks, physical care, health hazards, immunisations, malaria prophylaxis and travel medicines.

Conclusion

Air transport, by changing the face of travel-related illness from a rarity involving small, specific groups in society to a truly global problem, has led to a recognition of the importance of travel medicine. Even so, there is much more to be done before this recognition is translated into widely available effective services or to a proper awareness of the problem by travellers, travel companies and those who care for travellers.

References

1. Masterton, R.G. *et al.* (1991). *J. Appl. Bact.*, Symposium Supplement, **70:** 31S–38S.
2. Cossar, J.H. (1989). Wld. Hlth. Statist. Quart., **42:** 61–69.
3. Steffen, R. (1985). *Travel Med. International*, **3:** 76–79.
4. Jeannel, D. *et al.* (1991). *Br. Med. J.*, **303:** 336–338.
5. Bhopal, R.S. (1986). *Travel Med. International*, **4:** 189–193.
6. Weber, G. *et al.* (1990). *Trans. R. Soc. Trop. Med. & Hyg.*, **84:** 803–805.
7. Roberts, D. *et al.* (1989). *Environmental Health*, **97:** 56–62.
8. Burslem, C.D. *et al.* (1990). *J. Soc. Occup. Med.*, **40:** 97–100.
9. Tauxe, R.V. *et al.* (1987). *Am. J. Epidemiol.*, **125:** 150–157.
10. Vadhanasin, S. *et al.* (1976). *J. Med. Ass. Thailand*, **59:** 156–161.
11. Beers, K.N. *et al.* (1985). *Av. Space and Environ. Med.*, **56:** 594–597.
12. Tonks, A. (1992). *Br. Med. J.*, **304:** 733–734.
13. Phillips-Howard, P.A. *et al.* (1988). *Br. Med. J.*, **296:** 245–248.
14. Phillips-Howard, P.A. *et al.* (1990). *J. Epidemiol. Community Health*, **44:** 155–161.
15. Phillips-Howard, P.A. *et al.* (1990). *Br. Med. J.*, **300:** 499–503.
16. Majori, G. *et al.* (1990). *Trop. Med. Parasitol.*, **41:** 439–440.
17. Bateman, P.L.G. (1986). *Travel Med. International*, **4:** 193–197.
18. Russell, R.C. (1989). *Travel Med. International*, **7:** 26–31.
19. Bower, P. (1992). *Br. Med. J.*, **304:** 717.

There's more than just a new look to our Streptococcal Grouping Kit.

Now, as part of the new range of Oxoid Diagnostic Reagents, our Streptococcal Grouping Kit has been carefully redeveloped with your convenience in mind.

The first thing you will notice is the new packaging, but it doesn't stop there.

STREPTOCOCCAL GROUPING KIT

Inside is a cleverly designed and space saving work station which keeps all the elements of the kit together and secure.

Colour coded bottles now facilitate the selection of each grouping reagent.

And the new blue latex suspensions and white disposable reaction slides make interpretation of results easier, in any light.

The Oxoid Streptococcal Grouping Kit is already renowned for its unique and efficient enzyme extraction procedure and sensitive reagents which accurately identify all streptococcal groups, including group D in strains where D and G often cause misidentification.

So now, with these additional benefits, you will see that there's much more to our new Streptococcal Grouping Kit than meets the eye.

OXOID
Diagnostic REAGENTS
FROM UNIPATH

DESIGNED FOR CONVENIENCE

Unipath Ltd, Wade Road, Basingstoke, Hampshire RG24 0PW, UK. Tel: 0256 841144. Fax: 0256 463388. Telex: 858793. Telemessage: Unipath Basingstoke