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Antimicrobial Agents are Societal Drugs

How Should This Influence Prescribing?

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Abstract

This paper is concerned with how those who prescribe antimicrobials should consider the wider repercussions of their actions. It is accepted that in an ecological system, pressure will cause evolution; this is also the case with antimicrobials, the result being the development of resistance and the therapeutic failure of drugs. To an extent, this can be ameliorated through advances by the pharmaceutical industry, but that should not stop us from critically appraising our use and modifying our behavior to slow this process down.

Up to 50% of prescribing in human medicine and 80% in veterinary medicine and farming has been considered questionable. The Alliance for the Prudent Use of Antimicrobials (APUA) was approached by the WHO to review the situation. Their recommendations include decreasing the prescribing of antibacterials for nonbacterial infections. In the UK, there has been an initiative called 'the path of least resistance'. This encourages general practitioners to avoid prescribing or reduce the duration of prescriptions for conditions such as upper respiratory tract infections and uncomplicated urinary tract infections; this approach has been successful. Another recommendation is to reduce the prescribing of broad--spectrum antibacterials. In UK hospitals, the problems identified with the inappropriate use of antibacterials are insufficient training in infectious disease, difficulty in selecting empirical antibacterial therapy, poor use of available microbiological information, the fear of litigation and the fact that the majority of antibacterials are prescribed by the least experienced doctors. With close liaison between the laboratories and clinicians, and the development of local protocols, this can be addressed. Another recommendation is to tighten the use of antibacterial prophylaxis and to improve patient compliance. Through a combination of improved education for doctors and patients, and improved communication skills, these problems can be addressed. A further recommendation is to encourage teaching methods that modify prescribing habits. It has been shown that workshops have led to a significant reduction in the prescribing of broad-spectrum antibacterials in the community. Auditing the prescribing of antibacterials has also been recommended.

Surveillance systems around the world monitor trends in resistance: the European Antimicrobial Resistance Surveillance Progamme (EARSS) monitors antibacterial resistance; the WHO and the International Union Against Tuberculosis and Lung Disease collaborate to monitor tuberculosis; the WHO and the International AIDS Society monitor HIV.

In the third world, a bigger problem than resistance is whether drugs are even effective, as they are often spoiled by climactic conditions, and poor quality generics and counterfeit drugs are common. Also, patients may not be able to complete a course for financial reasons.

Facts about Antimicrobial resistance in Animals (and agriculture) and Impact on Resistance (FAAIR) was commissioned by APUA. They conclude that the nonhuman use of antibacterials can lead to the development of antibacterial resistance in human pathogens. The European commission banned the use of antibacterials as growth promoters in 1999.

In the Western world, we should improve our diagnosis of sepsis, access local guidelines and consider withholding treatment pending investigations, decide if treatment can be stopped earlier and treat the patient not the result. Many developing countries need improved access to more antimicrobials, preferably in the controlled environment of appropriate medical advice.

"*We need to relearn the use of antibiotics and advocate for a more controlled application of antibiotics for therapeutic use only so that strains susceptible to drugs will re-emerge.*" Dr Stuart Levy, President of the Alliance for the Prudent Use of Antibiotics (APUA)

This paper is concerned with how we can change the attitudes of both prescribers and consumers with regards to the use of antimicrobials. The problem is of resistance and poor quality use.[1] It is established that there is an association between antibacterial use and the prevalence of resistance.[2] Whether antibacterial control measures today can reduce levels of resistance is not so clear.[3]

1. Background

The use of antimicrobials is wide-ranging and differs from country to country;[4] they are consumed in human medicine, veterinary medicine, animal farming and agriculture. In the US, it has been quoted that 50% of antibacterial use is in human medicine, of which 80% is used in the community and 20% in hospitals; it has been suggested that 20–50% of prescribing is unnecessary.[5] Veterinary and farming use accounts for the remaining 50%, of which 20% is therapeutic and 80% is for prophylactic or growth promotion purposes; 40–80% of this usage has been questioned.[5]

The key to reducing inappropriate use of antibacterials is to develop guidelines for prescribers that generate a maximum health gain with a minimum development of resistance. The Alliance for the Prudent Use of Antibiotics (APUA), the European Society of Clinical Microbiology and Infectious Disease (ESCMID) and other authorities have made recommendations, working in partnership with the WHO. In this context, they are acting as stewards on an international level. There are also national and local stewards, such as Stichting Werkgroep Antibioticabeleid (SWAB) in the Netherlands and the Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance (STRAMA). In the US, the equivalents would be the Infectious Disease Society of America (IDSA) and the Center for Communicable Disease Control and Prevention (CDC). The European Centre for Disease Prevention and Control (ECDC) is a new European Union agency that opened in 2004 to provide stewardship in Europe against infections, including influenza, severe acute respiratory syndrome (SARS) and HIV. In the UK, most clinicians will follow local guidelines or refer to established references, such as the Monthly Index of Medical Specialties (MIMS) or the British National Formulary (BNF).

The dose is calculated by weight or age in children, but a standard does is generally used for all otherwise healthy adults. Prescribing schedules have been established by population studies, but this has tended to group variables together. It is evident that target organisms will have different minimum inhibitory concentrations and that the pharmacokinetics of drugs will be different in different patients. The result in an unlucky individual

(who is infected with a more resistant organism and in whom the peak concentration or the area under the curve is reduced) may be treatment failure as a result of sub-therapeutic antibacterial concentrations at the site of infection. The extent of this problem and its contribution to the global problem of antimicrobial resistance is yet to be established,[6] but we feel it is likely to be highly significant in selecting resistant strains.

The use of antibacterials outside standard regimens, such as prescribing long-term low-dose treatment, is also problematic. Guillemot and Carbon[7] showed convincingly that this led to an increased likelihood of penicillin-resistant pneumococci emerging in children. On the other hand, not finishing a course of antibacterials may be no bad thing, provided relapse of the infection is avoided. Even with adequate dosages, prolonged courses breed more resistance; therefore, the traditional advice to "keep taking the tablets" is no longer appropriate.[8]

The WHO wished to develop a global strategy for the containment of antimicrobial resistance. They sought a synthesis of recommendations from expert policy groups and approached the APUA. Their recommendations are based on the following four facets:

- The establishment of effective surveillance systems to assess the shift of antibacterial resistance patterns on a local, national and global scale, and use of this information to guide prescribers on the appropriate use of antimicrobials.
- The alteration of patient and provider behaviour to reduce the inappropriate use of antimicrobial agents.
- To encourage the research and development of new antimicrobial agents that can address the problems of established resistant organisms, and to treat infections caused by those that surveillance has indicated may cause future disease.
- To recognise the use of antibacterials outside human medicine. A comparable quantity is used in the farming industry and veterinary practice. The impact on this in human health is being assessed.

The recommendations of APUA on how antimicrobial prescribing should be influenced are as follows:

1. Reduce the prescription of antibacterials for infections that are not bacterial, i.e. viral upper respiratory tract infections.
2. Reduce the overprescription of broad-spectrum antibacterials.
3. Tighten the use of antibacterials in prophylactic situations, especially with respect to timing and duration.
4. Encourage patient compliance to prescriptions, including addressing the hoarding of antibacterials for future use.
5. Review the use of antimicrobial-containing cleaners and disinfectants.
6. Promote the use of non-antimicrobial interventions, such as condoms, bed nets with or without insecticide impregnation, and vaccination.
7. Encourage forms of teaching that are likely to result in modification of prescribing behaviour, these include interactive and repeated teaching sessions, such as workshops and problem-solving sessions.
8. Use of audit to monitor prescribing behaviour.[9]

As in all medicine, any guidelines that are produced should be evidence based. APUA has produced a comprehensive framework that can be followed with good clinical governance. While the evidence base behind these recommendations may not be confirmed by randomised clinical trials, they represent a synthesis of expert opinion and common sense.

There is the issue that antibacterials are drugs of fear, and perceived, rather than real, health risks lead clinicians to overprescribe broad-spectrum agents instead of observing the clinical development of symptoms pending the result of bacteriological investigations. The non-biomedical reasons for the overprescription of antibacterials have been investigated by Lam and Lam,[10] who found that, in the public sector, antibacterials were often prescribed as a time-saving measure. In the private sector, they were often prescribed for fear of losing clients.

To summarise, the relationship between the use of antibacterials and the development of resistance in humans and in the ecosystem we live in is problematic.[11] Current prescribing patterns indicate the problem can be improved through good control and stewardship. We need to consider how to change these patterns and to establish that improving pre-

scribing patterns will improve quality of use and reduce resistance.

2. Examples of Different Situations on a Global Scale

2.1 Human Medicine in Developed Countries, Using the UK as an Example

Of all antibacterials prescribed, 80% are in general practice; most of these are prescribed for respiratory tract infections, and the second most common reason for prescription is urinary tract infections.[12]

The common hospital pathogens tend to show the most resistant antibiogram and consist of meticillin-resistant *Staphylococcus aureus* (MRSA) and an assortment of Gram-negative bacilli. They are most problematic in the presence of a long-term prosthesis, a central line or a catheter, when the patient has been exposed to broad-spectrum antibacterials. It is generally accepted that someone has developed a hospital-acquired infection if sepsis develops >48 hours after admission.

2.1.1 APUA Recommendations

The following paragraphs discuss what is being done in the UK to alter prescribing behaviour, using APUA's eight recommendations as a framework (see section 1).

Reduce Prescription of Antibacterials for Nonbacterial Infections

To reduce prescription of antibacterials for infections that are not bacterial (i.e. viral upper respiratory tract infections in the community), there is an initiative named the Path of Least Resistance. The advice is not to prescribe antibacterials for sore throats, coughs or colds, to limit prescribing for uncomplicated urinary tract infections in healthy women to 3 days, and to limit the telephone prescribing of antibacterials. It appears that this has had an effect. The antibacterial prescribing rates in the community have fallen in England from 49.4 million scripts per year in 1995 to 36.9 million in 2000. The largest decrease has been seen in prescriptions for children.[13]

Reduce the Overprescription of Broad-Spectrum Antibacterials

Broad-spectrum antibacterials, such as amoxicillin/clavulanic acid and cefotaxime, tend to be prescribed when the patient is deemed to be septic; this is correct, as inadequate initial therapy will compromise patient outcome. In medical and surgical wards, however, only 70% of fever is due to infection, so an infection severity assessment is critical.[14] If the patient has been in hospital for >2 days, the possibility of a more resistant bacterial infection will be considered, so an extended-spectrum antibacterial may be considered. If the patient had MRSA recently and appears to be septic, then an antibacterial active against MRSA, such as vancomycin, teicoplanin or linezolid, will also be considered.

To reduce the overprescription of broad-spectrum antibacterials in the hospital setting, there is close liaison between the microbiologist and clinician with regard to positive cultures and, when asked for, other advice. The aim is to stop or narrow the spectrum of the antibacterial used as soon as investigations indicate what appropriate treatment may be. On the whole, the impact of this intervention is not as substantial as it could be because of poor or delayed communication of results. Where there are high prescribing rates of antibacterials in critically ill patients, such as an Intensive Care Unit (ICU), there are combined ward rounds to facilitate appropriate prescribing, with the most up-to-date results that may not yet be available on the computer. The antibacterial committee, comprising a microbiologist, an infectious disease clinician and a pharmacist, generates a list of restricted antibacterials that can only be prescribed after consultation with them. They establish a local protocol of appropriate first-line antibacterials for a given clinical scenario that targets the likely pathogens, with the knowledge of local sensitivity patterns. The antibacterial formulary is reviewed periodically. Another approach often considered is a mandatory review of intravenous antibacterials prescribed after 24–48 hours.[15] This is mainly to avoid inappropriately long courses of intravenous therapy but also serves as a prompt to review any positive microbiological results. Once a likely pathogen has been isolated, it is the responsibility of the clinician to

rationalise therapy. This is an area where there is room for improvement.

Problems identified in hospitals leading to the inappropriate use of antibacterials include, insufficient training in infectious diseases, difficulty in selecting the most appropriate antibacterial empirically, insufficient use of microbiological information available and the fear of litigation. Also, the majority of antibacterials are prescribed by the least experienced doctors.[14]

Tighten the Use of Prophylactic Antibacterials

To tighten the use of antibacterials as prophylaxis, the re-education of junior surgeons on an annual basis goes some way towards addressing this, but has by no means controlled it. Problems include inappropriate timing and duration of administration, along with confusion over what is the appropriate agent or agents to use. The Scottish Intercollegiate Guidelines Network (SIGN) has guidelines on this. It allows for input of local data to assess the appropriateness of prophylaxis in the local situation.[16]

Encourage Patient Compliance

To improve patient compliance with antibacterials in the community, patient education and the communication between doctor and patient must be improved. Communication skills is an area that has been highlighted at an undergraduate and postgraduate level in the UK in the last 10 years, with the introduction of role-playing scenarios and playing back video recorded consultations. Multimedia educational campaigns are being carried out in the UK. There was a two-phase campaign, with the first phase in the autumn of 1999 to support health professionals in the management of acute upper respiratory tract infections by reducing a patient's expectation for a prescription and encouraging the use of symptomatic relief. The second was in 2002 promoting the message that antibacterials kill good bacteria that keep us healthy. It used a combination of the press, magazines and media relations, and provided resource packs for schools and health authorities, and non-prescription pads to general practitioners and hospitals.[17]

APUA's fifth and sixth recommendations, the use of antimicrobial-containing cleaners and non-antimicrobial interventions, are not about prescribing so will not be addressed here.

Encourage Forms of Teaching that Modify Prescribing Behaviour

It is recognised that didactic teaching does not work as well as problem-solving workshops in modifying prescribing behaviour. A study has shown that antibacterial workshops have led to a 15.4% reduction in the prescribing of broad-spectrum antibacterials in the community.[18] The hospital environment, especially if it is a teaching hospital, is conducive to ongoing learning. For the more isolated doctors, perhaps in general practice, it might not be so easy to keep up to date. However, the advent of websites with guidelines should even the disparity. It is unrealistic to expect doctors to be up to date in all things, but it is reasonable for them to keep abreast of the current guidelines in the drugs that they most commonly prescribe, which include antibacterials. The Scottish Executive and the British Society of Antimicrobial Chemotherapy (BSAC) have funded a website for medical undergraduates to learn the prudent prescribing of antibacterials through a framework of learning objectives and reflective learning on a web-based format called 'appropriate antibiotic prescribing for tomorrow's doctor' (APT).[19]

Use of Audit to Monitor Prescribing Behaviour

The use of audit to monitor prescribing habits has been successful. Databases keep a record of antibacterials prescribed and are retrospectively analysed. In this way, individuals or departments can receive feedback and modify prescribing habits where appropriate. Computerised prescribing will allow easier audit without interfering with the prescribing process. A recent European-wide audit of hospital antibacterial prescribing is accessible at www.abdn.ac.uk/arpac.

In an ideal world, everyone with a bacterial infection requiring an antibacterial would have a firm microbiological diagnosis and the most narrow-spectrum antibacterial commenced for the minimum duration required for a cure. This is not the current situation and a degree of pragmatism is required to result in the majority of patients receiving appropriate antibacterial therapy.

To give an indication of the problem of clinically relevant resistant pathogens in Europe, there is useful information on the European Antimicrobial Resistance Surveillance Programme (EARSS) website

(www.earss.rivm.nl/) and the Antibiotic Resistance Prevention and Control (ARPAC) website (www.abdn.ac.uk/arpac). EARSS is an international network of national surveillance systems that collects comparable and validated antimicrobial susceptibility data for public health action. It collects information on *Streptococcus pneumoniae*, *S. aureus*, *Escherichia coli*, *Enterococcus faecalis* and *E. faecium,* which have been identified as causing invasive disease. It collects data from 600 laboratories serving 970 hospitals in 27 countries and has amassed data from 65 000 isolates. It is co-ordinated by the Dutch National Institute for Public Health and the Environment (RIVM).

The EARSS data on *S. pneumoniae* causing invasive disease were analysed to assess trends in resistance to penicillin and erythromycin from 1999 to 2002. Overall, the resistance to penicillin was 10% and to erythromycin, 17%. There was a decrease in penicillin resistance of 5.3% per annum, an increase in erythromycin resistance of 5.9% per annum and an increase of dual resistance of 7.6% per annum. EARSS predict that by 2006 there will be 20.4% resistance to erythromycin and 8.9% dual resistance.[20] ARPAC deals with a much broader selection of resistant bacteria, specifically regarding hospital infections and their control by antibacterial prescribing and infection control policies.

2.1.2 Tuberculosis

The incidence of tuberculosis in the UK is low. This is thanks to a highly effective national control policy. Where a patient has come from overseas, their country of origin is relevant, as it may be more likely that they have multidrug-resistant tuberculosis. In this situation, second-line agents should be used. Directly observed therapy can be used to ensure the treatment is taken. This is of greater relevance in undeveloped countries where people may be less inclined to complete a treatment course when they start feeling better.

The global project of anti-tuberculosis treatment-resistance surveillance has been in place since 1994. It is a collaboration between the WHO, the International Union against Tuberculosis and Lung Disease, and other partners. It has formed a network of supranational laboratories to aid national reference laboratories in quality assurance and susceptibility testing in conjunction with national or area anti-tuberculosis treatment-resistance surveillance.

The aims of this project are to estimate the magnitude and pattern of anti-tuberculosis treatment resistance, monitor trends, evaluate effectiveness of treatment programmes, plan and evaluate intervention and prevention programmes, aid in developing tuberculosis policies at a country level, strengthen laboratory services, advocate for increasing political commitment and identify research needs.[21]

2.1.3 Antivirals

The most commonly prescribed antiviral treatment for HIV is highly active antiretroviral therapy (HAART). It consists of two nucleoside reverse transcriptase inhibitors with either a non-nucleoside reverse transcriptase inhibitor or one or two protease inhibitors. The British HIV Association (BHIVA) produces treatment guidelines.[22] It is possible to carry out resistance testing. The patients with poor compliance will tend to select out the resistant viruses, which will result in an increasing viral load and treatment failure along with increasing their infectivity with resistant virus. This is an increasingly common problem. The global HIV treatment-resistance surveillance network is another WHO strategy for the containment of antimicrobial resistance.[23]

The treatment of tuberculosis and HIV have in common a longer duration of therapy compared with other infections. This makes patient compliance and the control of adverse effects all the more important.

2.2 Human Medicine in Developing Countries, Using Sub-Saharan Africa as an Example

The majority of morbidity and mortality in developing countries is in children <5 years old. They are dying of lower respiratory tract infections, malaria, bacillary dysentery and measles, as well as malnutrition. Other significant infectious diseases include HIV and tuberculosis.

The WHO has devised an Integrated Management of Childhood Illness (IMCI). This is a syndromic approach to clinical management. The antimicrobials used would depend on government policy. The range of antimicrobials is limited and the laboratory services are somewhat lacking. It is a

government's responsibility to ensure the knowledge of local antimicrobial sensitivity patterns is available and disseminated through District Medical Officers (DMOs). If a non-governmental agency is working in an area, they should liaise with DMOs and adhere to national guidelines.[24]

Most importantly, it must be ensured that medicines are still efficacious after transportation, given the climactic conditions. The temperature of a container exposed to the sun may rise to >50°C and spoil antibacterials. The appearance of counterfeit drugs, poor quality generics and the availability of antibacterials bought over the counter (OTC) are adding to morbidity in these countries. The counterfeit or generic drugs may be less efficacious, and the OTC antibiotics may be taken for too short a time or in too low a dosage because of expense.

A background document for the WHO global strategy for the containment of antimicrobial resistance called Drug Resistance in Malaria concludes that people need more access to antimalarials.[25] It is accepted that this will lead to increasing levels of resistance, so there must also be investment in control measures to increase the useful lifespan of a therapy, and to allow time for new treatments and controls to be developed.

The problem with prescribing for tuberculosis is compliance with therapy. The WHO feels so strongly about this that they advise not to commence treatment if supervision over the full duration of therapy can not be assured (usually 6 months). This is of particular relevance in the refugee setting.

The use of non-antimicrobial interventions is mainly targeting malaria (with bed nets) and HIV (with low-priced condoms), and a national vaccination programme (which is incorporated into the IMCI).

2.3 Non-Human Uses of Antimicrobials

Dr Calvin Schwabe talks of 'One Medicine', the bringing together of human and veterinary medicine. "Human health provides the most-logical unifying or apical cause in veterinary medicine's hierarchy of values. Veterinarians in all aspects of the profession have opportunity and responsibility to protect the health and well-being of people in all that they do, including protecting food security and safety; addressing threats to antibiotic sensitivity; preventing and controlling zoonotic emerging infectious diseases; protecting environments and ecosystems; participating in bio- and agro-terrorism preparedness and response; using their skills to confront non-zoonotic diseases (such as malaria, HIV/AIDS, vaccine preventable diseases, chronic diseases and injuries); strengthening the public-health infrastructure; and advancing medical science through research."[26]

Veterinary practice uses an equivalent quantity of antimicrobials to human medicine, but mainly for growth promotion and disease prevention. Common therapeutic uses include treating mastitis in dairy cattle and respiratory illnesses in battery-reared chickens. Non-therapeutic uses include growth promotion in chickens. In agriculture, streptomycin and oxytetracycline are used to spray fruit in orchards to make them more visually appealing. To investigate this situation further, the APUA initiated a 2-year project called Facts about Antimicrobial resistance in Animals (and agriculture) and the Impact on Resistance (FAAIR).[27] It is concerned with the overall effects of antimicrobial use from an ecological point of view. There are two ways they consider that resistant infections can be acquired from the environment; the first is from direct infections from human pathogenic bacteria, such as salmonella from chickens, and the second is from the human acquisition of resistant nonpathogenic bacteria from the environment, which can act as a reservoir of resistance genes that maybe transferred to human pathogenic bacteria. The findings and conclusions are that antimicrobial use selects resistant bacterial strains and genetic vectors specifying resistance genes. The authors see the propagation of antimicrobial resistance as an ecological problem and suggest that reducing it would require an understanding of the commensal microbiota of mammals and genetic vectors of resistance. When one antimicrobial selects out resistance, because of the genetic linkage of resistance genes, other antimicrobial resistances will emerge. The period between the use of an antimicrobial and the emergence of resistance varies, but once the prevalence reaches a certain level, reversal is difficult. The effect of this on the global problem of antimicrobial resistance is unknown. FAAIR's conclusions are that any antimicrobial

used anywhere for anything can affect anyone anywhere in the world. This will cost us financially and our health may be affected, although at a population level the cost of antibacterial resistance is not known. Therefore, the elimination of the nontherapeutic use of antimicrobials in food animals and agriculture will benefit us all. The European Commission banned the use of antibacterials as growth promoters in 1999.

Several groups are looking into ways to evaluate the safety of ingested antimicrobial residues used in veterinary medicine on the human intestinal microflora.[28] One group has identified the presence of multidrug-resistant enteric bacteria in dairy farm topsoil and implicated this as a reservoir for bacterial resistance against clinically relevant antibacterials.[29] The problem of resistance can be further compounded by the handling of waste from food animals which will often pollute a widespread area by contaminating water supplies. Food animals may also develop antibacterial-resistant diseases but the scale of the problem has not been ascertained. The mechanism of increased disease in humans from antimicrobial resistance in animals is multifactorial and includes an increase in colonisation rates, an increase in pathogenicity and a decrease in the efficacy of treatment.[27]

3. Conclusions

Antimicrobials are unique amongst all drugs in that their use can result in reduced efficacy. In many areas, there is room for improvement in the way they are used. How should this influence prescribing? For a medicine to be prescription-only implies an established infrastructure of healthcare that does not necessarily exist in many developing countries. Indeed, not all developed countries have legislated antimicrobials to be prescription-only in human medicine and in farming. Developed counties have a cultural fear of microbes and perhaps the promotion of products that 'kill all known germs dead' only encourages this. However, the tide is turning and people are becoming more understanding that not all 'germs' are bad. The fact that children are brought up so hygienically has raised the question of whether this increases the development of allergic conditions and impairs immunity.

Prescriber's attitudes cover a spectrum from conservative to aggressive. The use of antimicrobials is easily justified in life-threatening conditions, but often they are prescribed to reduce morbidity and prevent the occasional complication. The word 'doctor' is derived from the Greek word for 'teacher'. It is important to educate patients about the condition they have as fear is usually a result of ignorance. Reassurance and addressing why a problem is occurring or recurring should not be forgotten. For developed countries, we should influence our prescribing in five ways:

1. Improve our diagnosis of sepsis.
2. Access the latest local guidelines on the subject.
3. Decide if antimicrobial treatment can be withheld pending positive microbiology.[30]
4. Decide if treatment can be stopped or rationalised once results return and chase up results if they are not received on time.
5. Treat the patient, not the results.

Advances in information technology and near patient testing could also improve prescribing behaviour.

Many developing countries need improved access to more antimicrobials preferably in the controlled environment of appropriate medical advice.

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