

Medicines regulation - National

David Legge

Savar, November 2018

(Several slides from Ken Harvey gratefully acknowledged)

National regulation

- Licensing of manufacturers and certification of foreign manufacture (GMP – good manufacturing practice)
- Approval / notification of clinical trials
- Registration of medicines / marketing approval
 - pre-approval evaluation
 - post-approval pharmacovigilance
- Labelling and packaging
- Advertising, promotion, guidelines, advice
- Prescribing and use / quality use of medicines
- Price regulation
- Subsidy and public procurement (EML - essential medicines lists); institutional procurement
- Shortage notification and response

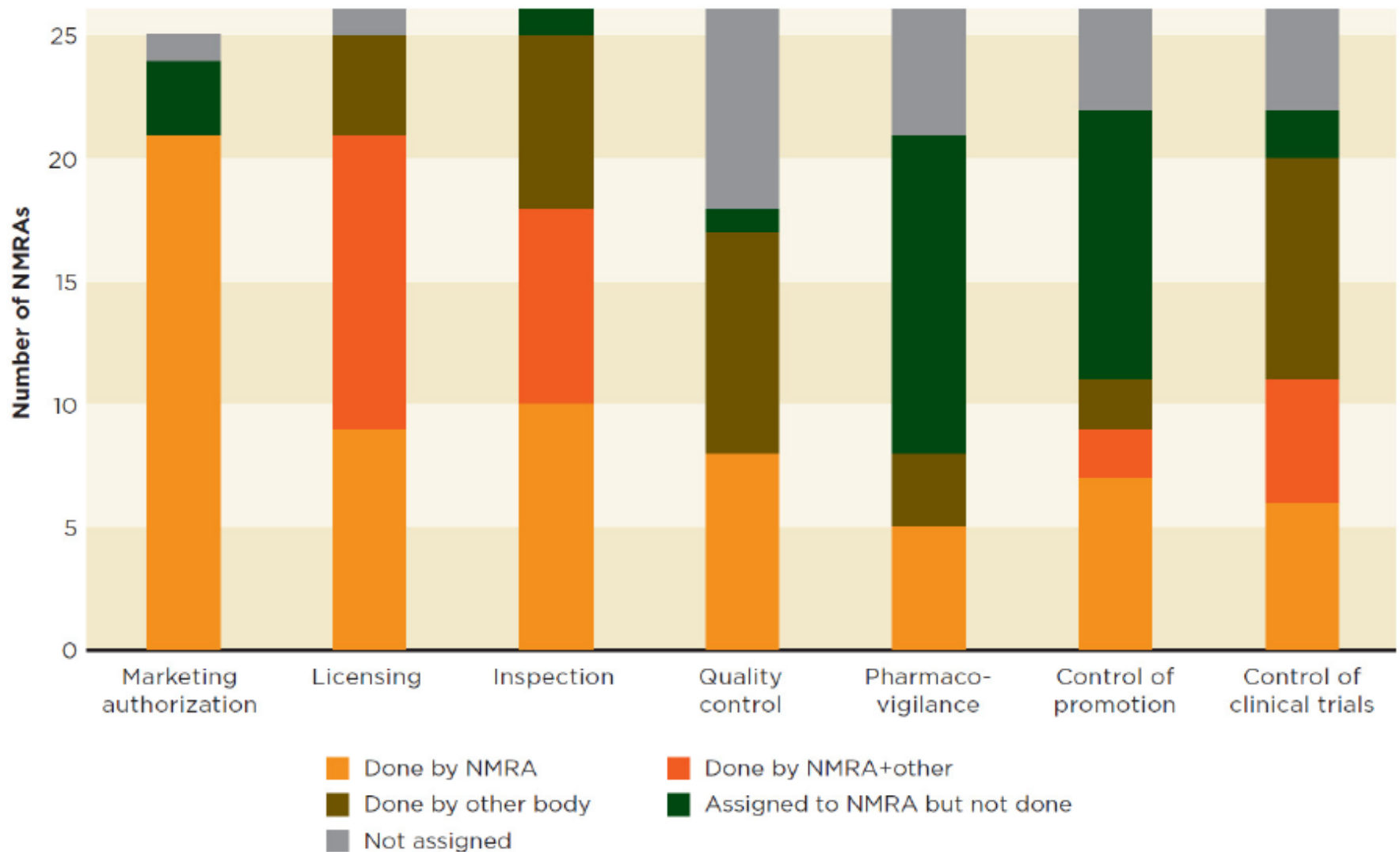


FIGURE 4-4 Number of sub-Saharan African countries out of 26 surveyed meeting the main functions of a regulatory authority.

NOTE: NMRA = National Medicines Regulatory Authority.

SOURCE: WHO, 2010a.

Health systems strengthening

- Universal health cover including social pooling to cover the cost of medicines
- Effective bulk purchasing, tight health system logistics, contract solutions to production and distribution shortfalls
- Clinical governance including clinical guidelines and quality assurance

Data for marketing approval

- Quality data
 - composition of the drug substance and the drug product
 - batch consistency
 - stability data
 - sterility data (if applicable)
 - the impurity content
- Nonclinical data
 - pharmacology data
 - toxicology data
- Clinical data
 - results of clinical trials
 - results of post-approval surveillance
- Risk management plan (pharmacovigilance)

Pharmacovigilance

- Risk management plan
 - analysis (and review) of safety profile of drug
 - initial drug evaluation data for marketing approval
 - monitoring activities
 - routine
 - additional
 - risk minimisation activities
 - routine
 - additional

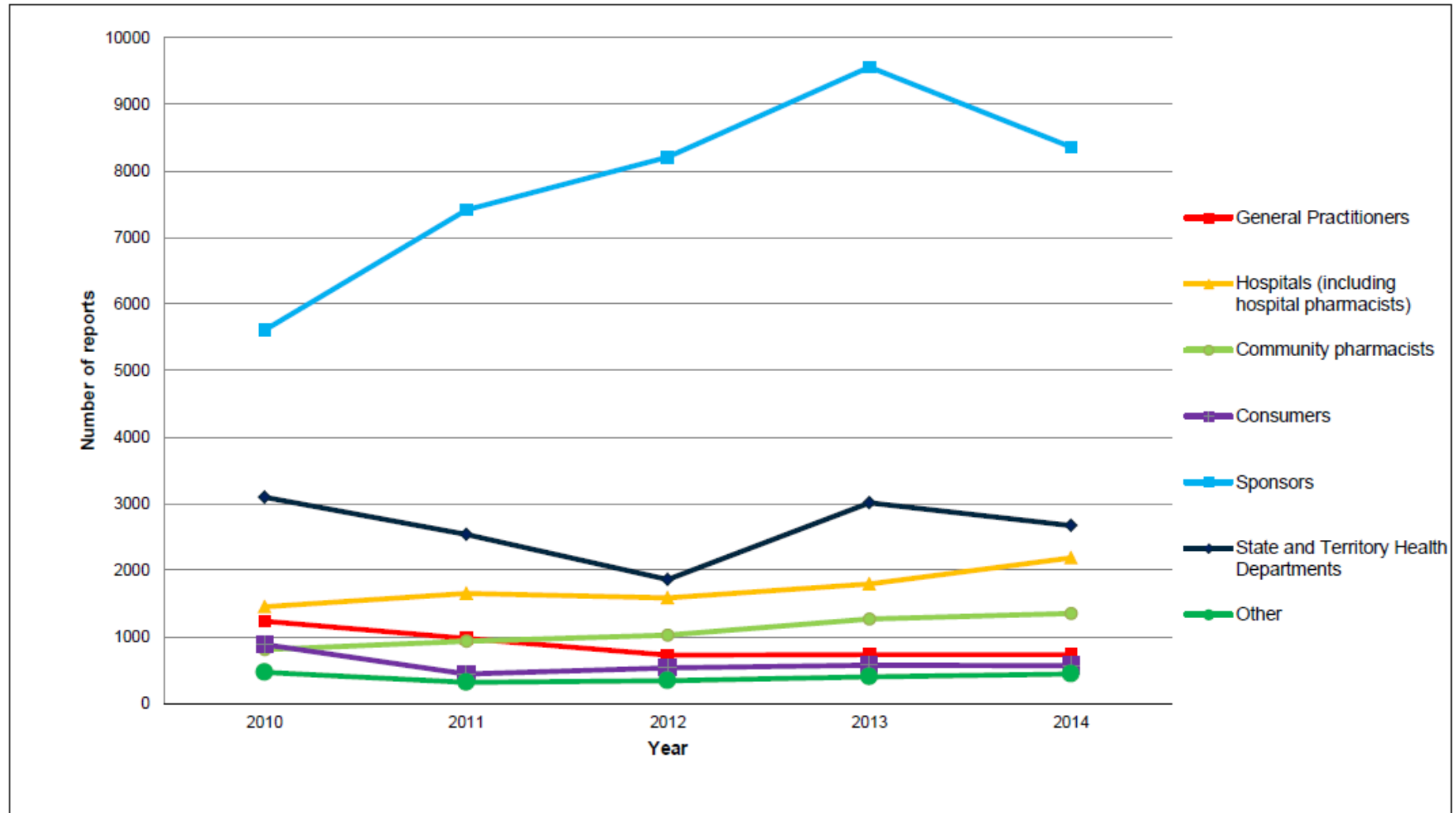
Risk monitoring

- Routine
 - evaluation for approval
 - adverse event reporting
 - periodic update safety reports
 - identification and analysis of safety signals (eg WHO product alerts)
- Additional
 - clinical trials
 - post-authorisation safety studies
 - drug utilisation studies
 - patient registries
 - physician surveys
 - prescription event monitoring

Risk minimisation

- Routine
 - product information
 - consumer medicine information
 - directions for use document
 - labelling, pack size and design
 - legal (prescription) status
- Additional
 - education programs
 - prescriber checklists
 - DHCP letters
 - controlled access programs
 - medical software alerts

Volume of adverse event reports received by the TGA (2010-2014)





Example – lumiracoxib cancellation

- Lumiracoxib:
 - registered July 2004
 - COX-2 inhibitor, not the first in class
 - PBS subsidy August 2006
 - 60,000 users.
- Eight reports of serious hepatotoxicity, with two deaths and two transplants.
- Registration cancelled August 2007.
- Liver death (fatality or transplant) 1 in 15,000:
 - rule of 3: would need 45,000 in a trial
 - therefore, impossible to detect premarket
 - but a significant risk considering underlying disease, efficacy and availability of alternatives.

Inappropriate use

- Impact
 - over use
 - wrong treatment
 - inadequate treatment
- Causes
 - doctors' lack of information
 - doctors' lack of commitment to evidence based practice
 - aggressive marketing
 - weak regulation
 - consumer pressure
- Necessary background
 - medicines promotion; principles, precedents and politics
 - professional education
 - struggles over medicines regulation
 - community attitudes and expectations

WHO (2002)

- Worldwide more than 50% of all medicines are prescribed, dispensed, or sold inappropriately, while 50% of patients fail to take them correctly.
- Common types of irrational medicine use are:
 - the use of too many medicines per patient (polypharmacy);
 - inappropriate use of antimicrobials, often in inadequate dosage, for non-bacterial infections;
 - over-use of injections when oral formulations would be more appropriate;
 - failure to prescribe in accordance with clinical guidelines;
 - inappropriate self-medication, often of prescription only medicines.

Inappropriate prescribing for the elderly

- Brazil (60+ years, discharged from tertiary hospital)
 - 13.9% potentially inappropriate medications
 - 39.1% potential prescribing omissions
- Los Angeles (400 elderly African Americans)
 - 70% potentially inappropriate medications
 - 27% taking at least one medication classified as “Avoid”
- US Veterans Health Administration (older adults receiving OP care)
 - 12.3% potentially inappropriate prescriptions

Inappropriate antibiotic use (WHO, 2005)

- In industrialized countries, around 80-90% of antibiotic use for humans occurs in the community
 - at least half of this is based on incorrect indications, mostly viral infections
 - contributing to widening threat of resistance
- Extensive use of antibiotics in livestock production contribute to spread of resistance
- Antimicrobial resistance plus reduced R&D threatens a 'post-antibiotic era'

Medicines promotion

- Aggressive marketing of under-patent drugs standard practice
 - maximise revenues before patent expires
 - embed brand name familiarity to maintain price premium after patent expires
- Includes
 - public relations
 - advertising
 - direct marketing ('medical representatives')
- Spending 50-100% more than on R&D
- Benefits and risks
 - rapid translation of therapeutic advances into practice
 - encourages over-servicing and inappropriate prescribing
 - drives cost escalation
 - builds community expectations: 'a pill for every ill'
- WHO 'Ethical criteria'
- National regulatory norms
 - principles and precedents
- Politics and debates

WHO: ethical criteria for drug promotion

- ... claims concerning medicinal drugs should be reliable, accurate, truthful, informative, balanced, up-to-date, capable of substantiation and in good taste
- [promotional material] should not contain misleading or unverifiable statements or omissions likely to induce medically unjustifiable drug use or to give rise to undue risks
- The word "safe" should only be used if properly qualified. Comparison of products should be factual, fair and capable of substantiation.
- Promotional material should not be designed so as to disguise its real nature.
- Scientific and educational activities should not be deliberately used for promotional purposes.
- Advertisements to the general public ... should not generally be permitted for prescription drugs or to promote drugs for certain serious conditions that can be treated only by qualified health practitioners.

Common practices

- Advertising
- Public relations
- Medical detailing
- Advertisements within prescribing software
- Gifts (equipment, travel, accommodation, etc)
- Sponsored dinners, recreational events
- Conference sponsorship
- Journal support through advertising
- Sponsored research
- Sponsored clinical guidelines
- Consultancies and advisory boards
- Ghostwriting
- Support for patient associations
- Disease mongering (meetings, media, reports)

Disease mongering



PLoS Medicine. A collection of articles on disease mongering: how drug companies sell sickness. Presented at the Inaugural Conference on Disease Mongering, Newcastle, Australia, April 11-13, 2006. <http://collections.plos.org/diseasemongering-2006.php>

Drug Promotion: Why the concern?

Drug giant forks out \$65,000 on posh nosh for doctors

The Australian, July 21, 2006



- Pharmaceutical promotion selectively promotes the benefits of the latest and most expensive drugs.
- It provides minimal information about drug side-effects, contra-indications and opportunity costs.
- Cost-effective generic drugs and non-drug solutions are rarely promoted.

“Pigs and reptiles”



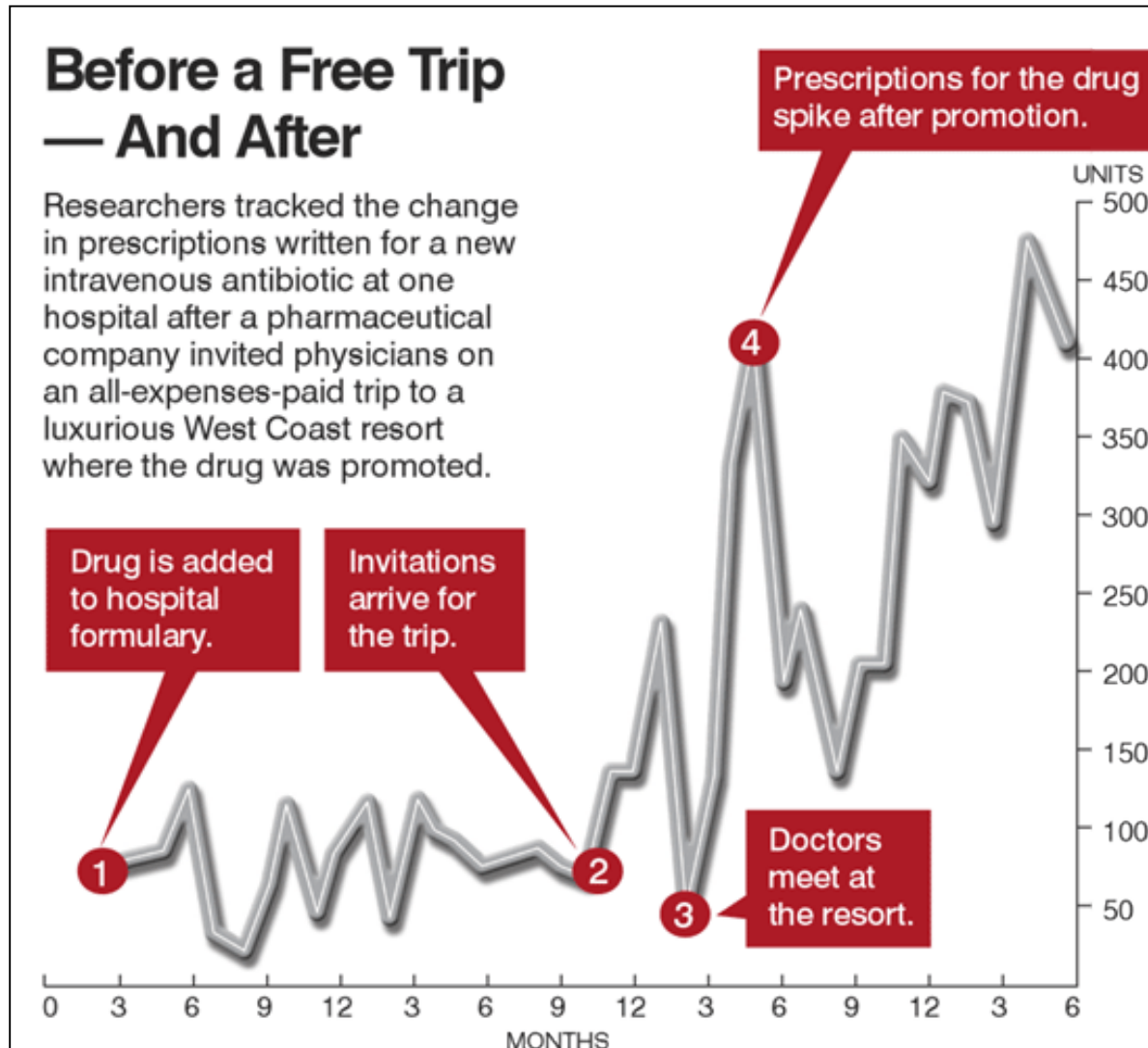
- Some 80-95% of doctors regularly see drug reps despite evidence that their information is overly positive and prescribing habits are less appropriate as a result.
- Many doctors receive multiple gifts from drug companies every year, yet most doctors deny their influence despite considerable evidence to the contrary.

BMJ 2003;326 (31 May)

However

- Industry-doctor interaction correlates with:
 - doctors' preferences for new products that hold no demonstrated advantage over existing ones.
 - decreased prescribing of generic drugs.
 - a rise in both and irrational and incautious prescribing.
 - rising prescription expenditures.

“Pigs and reptiles”



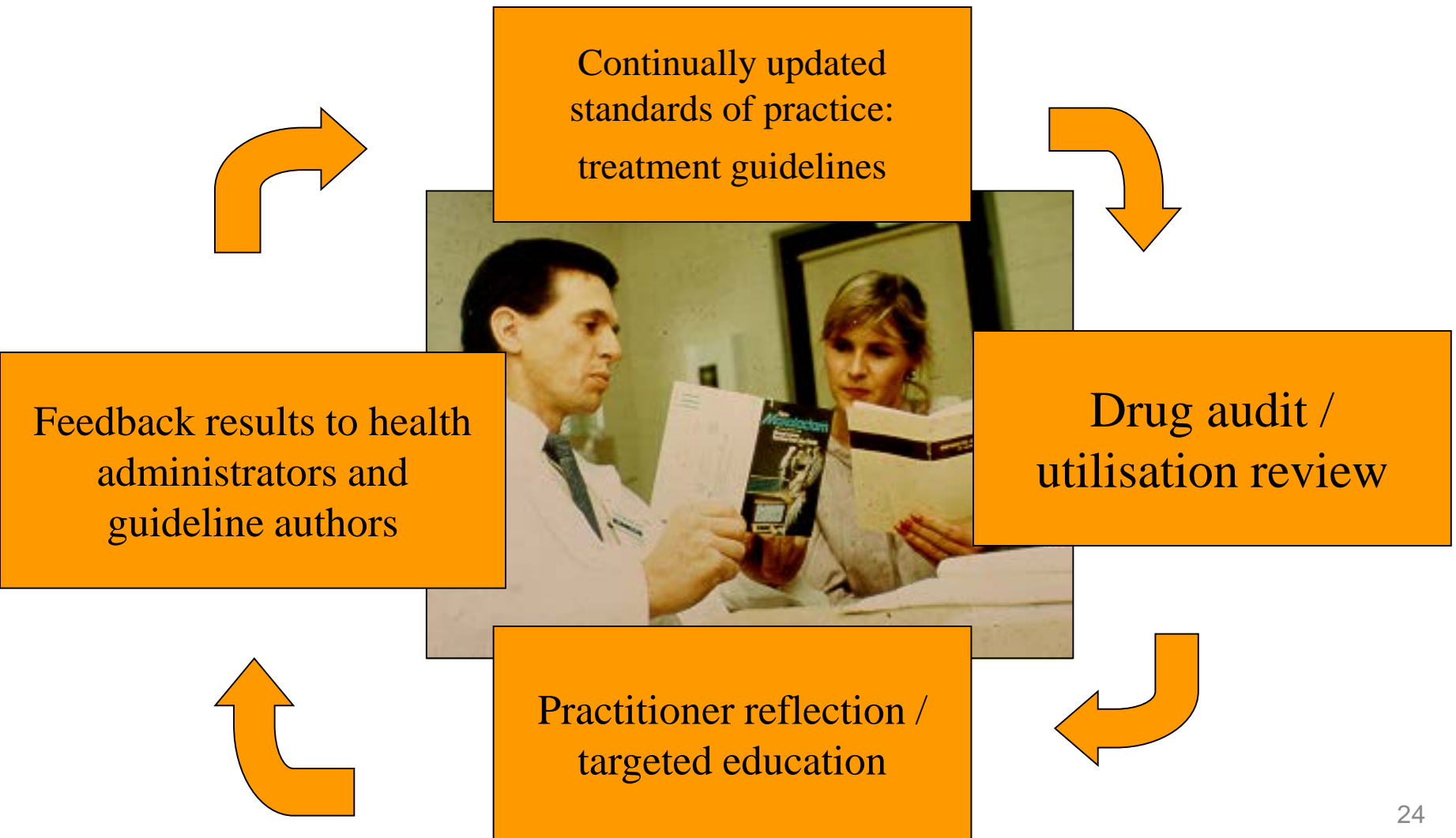
Independent information

The collage features several key Australian medical resources:

- RADAR (Rational Assessment of Drugs and Research)**: Logo at the top left.
- Therapeutic Guidelines (TG Complete)**: A screenshot of a Microsoft Internet Explorer browser window showing the website's contents menu. The menu includes: Help, Key information, Licence agreement, What's new in Therapeutic Guidelines, Feedback, About Therapeutic Guidelines, Abbreviations, Preface to TG: Complete, Analgesic, Version 3, 1997, Antibiotic, Version 11, 2000, Principles of antimicrobials, Getting to know your cardiovascular system, and Cardiovascular system.
- Australian Adverse Drug Reactions Bulletin**: A large blue box with the title in white text.
- Schedule of Pharmaceutical Benefits**: A yellow box with the title in black text.
- australianprescriber**: A black box with the title in white text, with "prescriber" in a larger font. Below it, it says "An Independent Review".
- Australian Medicines Handbook Online**: A logo at the bottom left consisting of stylized letters "AMH" with a pill icon.
- Other Resources**: Several smaller boxes representing Therapeutic Guidelines for Antibiotic, Analgesic, Dermatology, and Endocrinology, each with a representative image.

澳大利亚药物不良反应通报

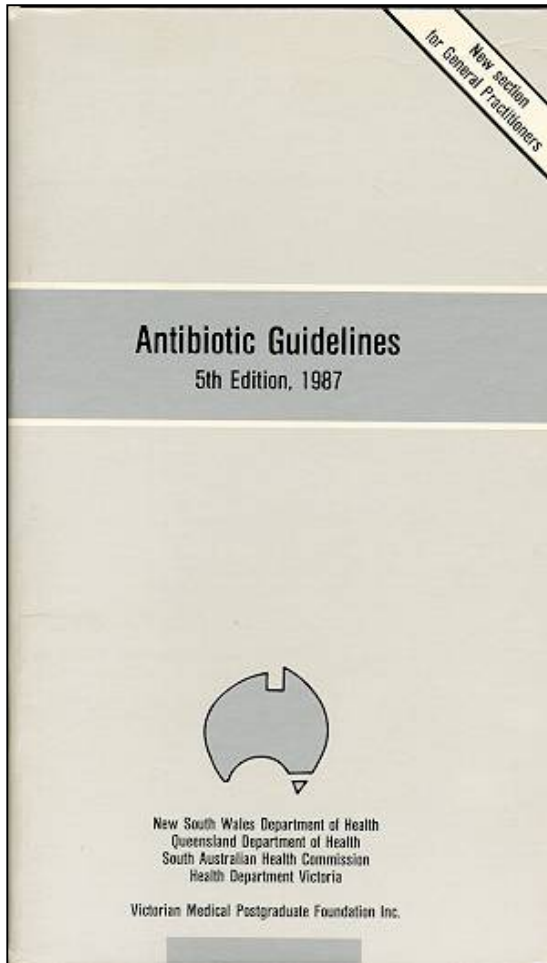
Quality Assurance Cycle



Independent advice

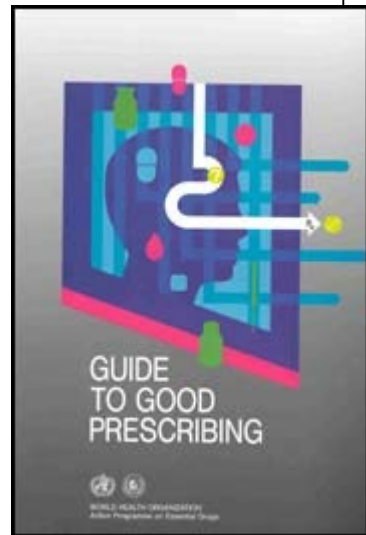
- Invest in provision of independent advice;
 - professionals (including clinical guidelines, academic detailing);
 - consumers (including social marketing) (inappropriate use)

Antibiotic Guidelines



- Best practice recommendations concerning the treatment of choice for common clinical problems.
- Written by teams of national experts.
- Evidence based where possible.
- Regularly updated.
- Endorsed by Medical Associations, Colleges, etc.
- Used for medical education, problem look-up, drug audit and targeted educational campaigns.

NPS: Core curriculum



NPS
National Prescribing Service Limited

Help | Contact us | Feedback | Administration
Copyright | Disclaimer | Privacy

Click Here to Log-in))

Sponsored by
ASCEPT

Australian Society of Clinical & Experimental
Pharmacologists and Toxicologists

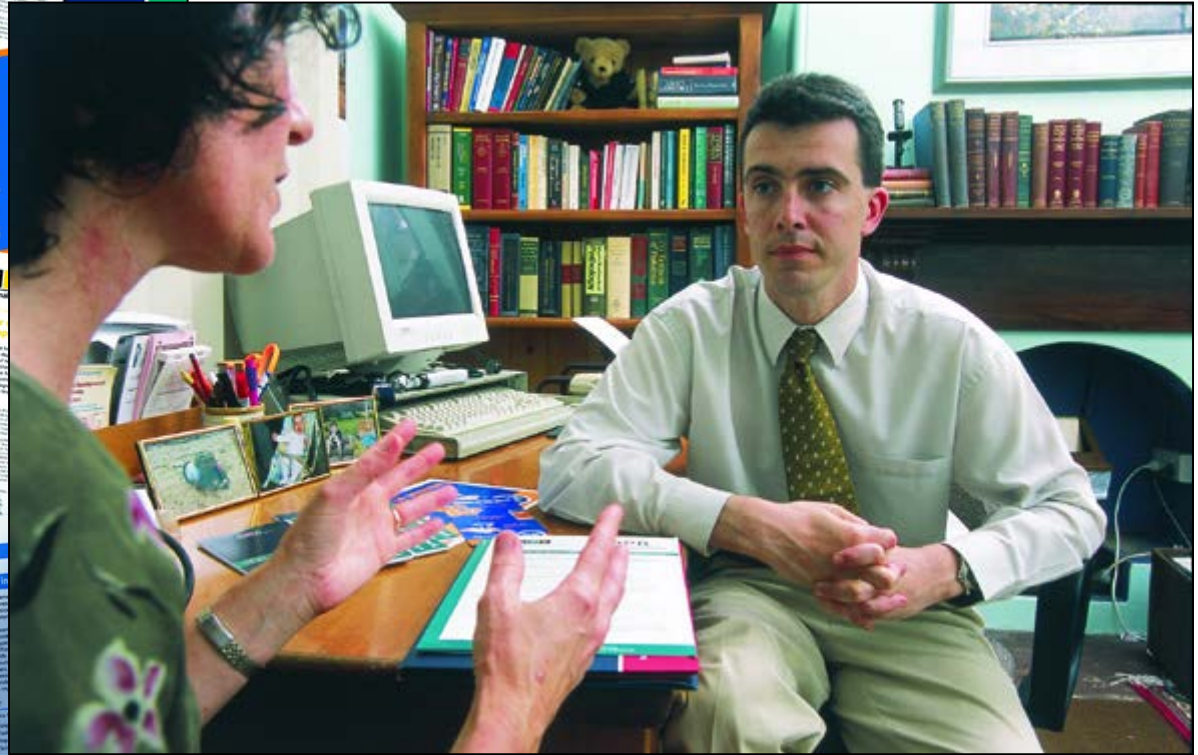
National Curriculum Promoting
Better Prescribing

Guests may log into the website by
clicking the main link above. Type 'visitor'
as both your username and password.

<http://nps.unisa.edu.au/new/index.htm>

NPS: Academic detailing

Also: home medication review by pharmacists



NPS: Consumer Campaigns

The difference between common colds and flu

Common cold

Symptoms include a runny or blocked nose, sneezing, minor throat irritation, mild fever and a feeling that your ears are blocked. Coloured mucus or nasal discharge does not mean you are getting worse – it means your immune system is fighting the infection.

Flu

Influenza is a much more serious illness. Often people call a 'common cold' the 'flu', but they are different illnesses. Symptoms usually start suddenly with a high fever and you may feel sick enough to go to bed. Symptoms include irritation in the throat or lungs, a dry cough, high fever, shivering, sweating and severe muscle aches. The flu tends to make the whole body ache, whereas the common cold usually affects the nose and throat only.

Influenza vaccinations are available and recommended for older people, people with chronic illnesses, pregnant women and people who live in nursing homes. Ask your doctor for more information.

Medicines to treat influenza are available by prescription from your doctor. They have no benefit in the common cold.

When to see a doctor

See your doctor if your symptoms are severe, last longer than usual or if you have any of the following symptoms:

- severe headache or a stiff neck
- your eyes hurt when exposed to light
- you have difficulty waking up
- a skin rash
- a fever that lasts longer than three days
- vomiting
- a child develops high fever, a strange/high-pitched cry or skin rash
- shortness of breath or difficulty breathing.

See your doctor if you are worried. Your doctor can check the severity of your illness, tell you how long it may last, give advice on treatment and provide you with a medical certificate if needed.

National Prescribing Service Ltd (NPS)

NPS is a non-profit, independent organisation working to improve the health of Australians through appropriate prescribing and use of medicines. With 35 peak health bodies as members, NPS works in partnership with GPs, pharmacists, specialists, other health professionals, Government, pharmaceutical industry, consumer organisations and the community.

**Antibiotics
won't help a
common cold.
Common
sense will.**



**Take it
easy.**



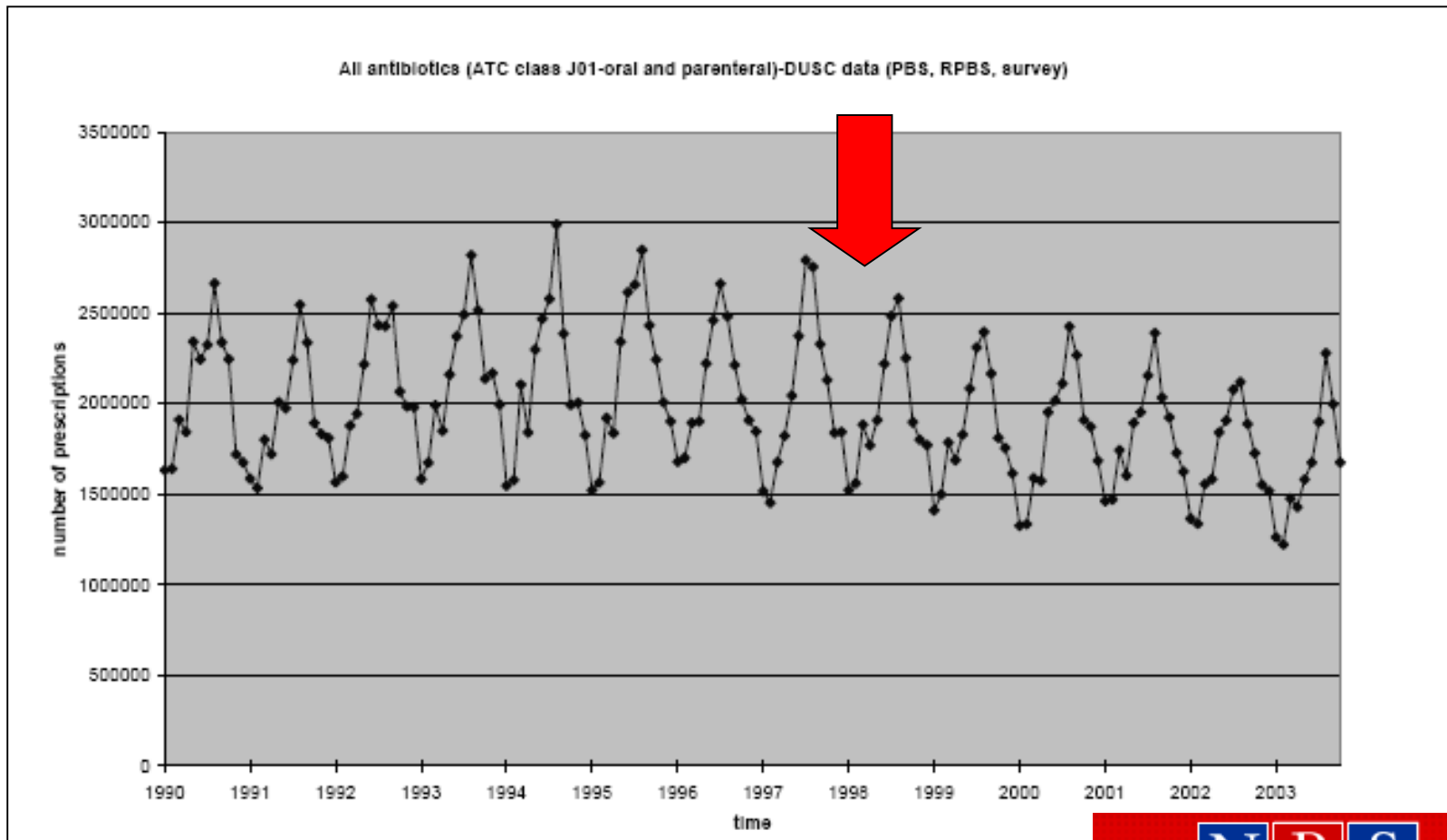
**Drink plenty
of fluids.**



**Treat your
symptoms.**

© 2003

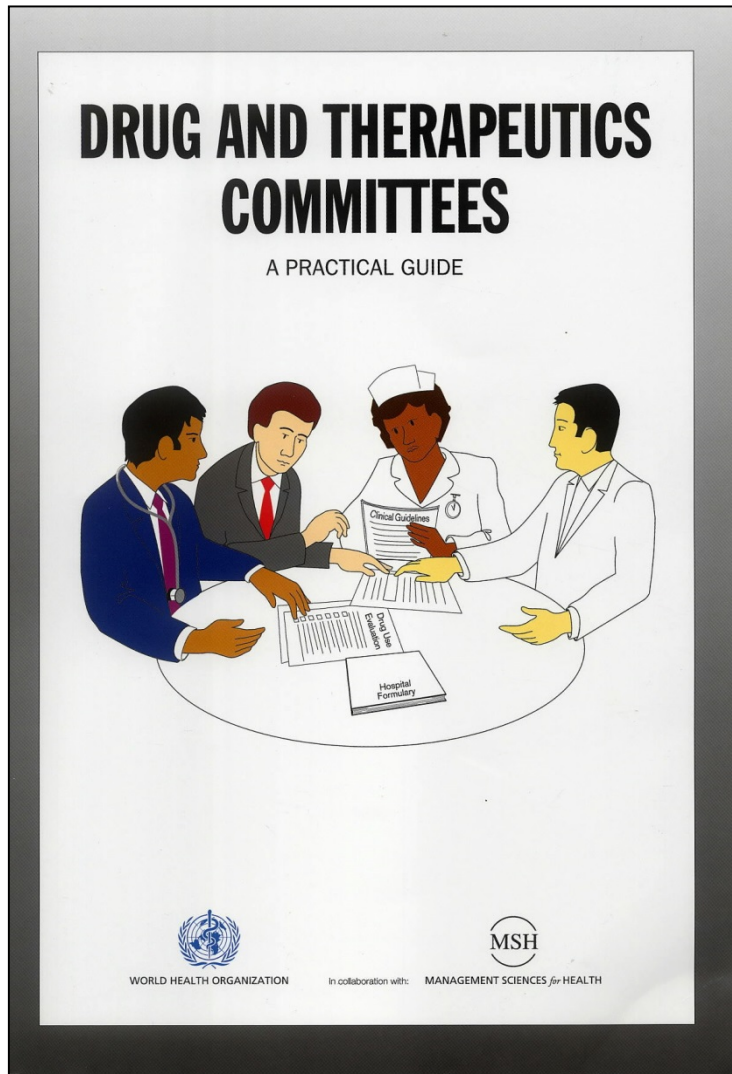
Results: antibiotics scripts 1990-2004





- The NPS initially received about \$5 million per annum (for four years) in 1997/98.
- A evaluation of their first three years of operations suggested their activities achieved PBS savings of over \$15 million per annum for a cost of \$5 million per annum.
- Their budget has subsequently been increased and a consumer education moiety has been added.
- Spending money on RDU activities saves money by reducing inappropriate drug use.

In hospitals: drug and therapeutics committees (DTCs)



- Select cost-effective drugs for the hospital formulary.
- Develop (or adapt) and implement standard treatment guidelines.
- Audit drug use to identify problems.
- Conduct interventions to improve drug use.
- Manage adverse drug reactions and medication errors.
- Educate staff about drug use issues, policies and decisions.