**WHEN THINGS GO WRONG**

Randomised controlled trials are not the only source of evidence. Cohort studies (Bandolier 23,24) can provide valuable information, especially when things go wrong - with rare but serious adverse events, for instance.

An interesting example of such a cohort study was published in JAMA last year [1]. This Boston investigation set out to assess the incidence and preventability of adverse drug events (ADEs) and potential ADEs and to analyse these events in order to develop prevention strategies.

**Not as rare as you may think**

Answer the following question. Do you think that ADEs in hospitals in the USA, compared with road traffic accidents in the USA, are the cause of:

- A: many fewer deaths?
- B: about the same number?
- C: many more?

According to the introduction to the paper [1], which summarises some of the information about this, the correct answer is C. Roads are safer in the UK, so the same answer to the same question is even more likely in the UK.

**Adverse drug event**

An ADE is defined as an injury resulting from medical intervention relating to a drug. This definition is different from that of an adverse drug reaction (ADR), defined by WHO as “noxious and unintended, and which occurs at doses used in man for prophylaxis, diagnosis or therapy”. The ADR definition is likely to be idiosyncratic and rare, and would, for instance, not include an unintended misprescription of a larger than therapeutic dose of a drug which caused harm because it was an overdose. Such an event would be an ADE. It should not occur and is likely to be preventable.

**Setting**

All adults at the Brigham and Women’s Hospital (726 beds) and Massachusetts General Hospital (846 beds) admitted to any of 11 units over six months were included in the study. Obstetric units were not included. The 61 non-obstetric adult units were stratified between hospital, whether medical or surgical and whether intensive or general care. Study units were then selected randomly using a random number generator.

**Method**

Three methods were used to identify incidents:

1. Nurses and pharmacists were asked to report incidents to nurse investigators.
2. A nurse investigator visited each unit twice daily on weekdays to solicit information.
3. The nurse investigator reviewed all charts at least daily.

The primary outcome was an ADE, and a secondary outcome a potential ADE (an example would be a patient with known sensitivity to penicillin who was given penicillin, but did not react). To discover the cause of preventable ADEs, persons involved were interviewed and the results investigated by a multidisciplinary team.

All incidents were evaluated independently by two physicians who classified them according to the following criteria: whether or not an ADE or potential ADE had occurred, severity, preventability and, if an error had occurred, the type of error and the stage in the process at which it occurred. Reviewers were asked to consider ADEs as preventable if they were due to an error or were preventable by any means currently available.

**Results**

In the study period, there were 4,031 admissions to the study units, comprising 21,412 patient-days (about 10% of the 214,000 patient days in adult, nonobstetric units at the two hospitals).

The study found 247 ADEs and 194 potential ADEs. Extrapolated, this amounted to 1900 ADEs per hospital per year, with, for every 100 admissions, 6.5 ADEs and 5.5 potential ADEs. Of all ADEs, 1% were fatal, 12% life-threatening, 30% serious and 57% significant.

The rate of ADEs was highest in medical intensive care units (19 per 1,000 patient-days) and relatively similar among surgical intensive care and medical and surgical general care units (9 - 11 per 1,000 patient-days).

Over 50% of all ADEs were associated with the use of analgesics (30%) or antibiotics (24%). No single drug accounted for more than 9% of ADEs. Analgesics were the leading drug class associated with preventable ADEs, and half of these involved misuse or malfunction of infusion pumps or devices (epidural catheters or patient-controlled analgesia).

The Table shows the data by actual numbers in the study, by the rate per 100 admissions, and by extrapolation to events per hospital per year. It is instructive that even the lowest of these event rates adds up to a significant number of patients.
<table>
<thead>
<tr>
<th>Event</th>
<th>Number</th>
<th>Rate per 100 admissions</th>
<th>Number per hospital per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ADEs</td>
<td>247</td>
<td>6.5</td>
<td>1923</td>
</tr>
<tr>
<td>Due to analgesics</td>
<td>73</td>
<td>1.9</td>
<td>568</td>
</tr>
<tr>
<td>Due to opiates</td>
<td>57</td>
<td>1.5</td>
<td>444</td>
</tr>
<tr>
<td>Preventable ADEs due to pump or device malfunction</td>
<td>9</td>
<td>0.2</td>
<td>70</td>
</tr>
</tbody>
</table>

**Preventable ADEs**

Seventy (28%) of 247 ADEs were preventable and 83 (43%) of 194 potential ADEs were intercepted before the drug was given. Errors resulting in preventable ADEs occurred most often at the stages of ordering (56%) and administration (34%); transcription and dispensing errors were uncommon. Errors were more likely to be intercepted if they occurred early in the process - 48% at the ordering stage but none at administration of the drug.

**Cost**

ADEs generate costs to the patient, costs to the hospital though treating the effects of the ADE, and costs (at least potentially) of medical negligence claims. The hospital cost alone was estimated to cost $2,000 per event - making about $3.8 million per hospital per year. $1 million of this was preventable today, notwithstanding the human cost.

**Lesson**

How might a hospital improve the quality of its drug delivery process? To get the full flavour of the lessons from this study, read the paper and some of the many useful references. In précis the lessons are:

1. Have an effective mechanism for systematically collecting and feeding back data about ADEs.
2. The organisation must look for preventable ADEs, not just ADRs.
3. System change must be directed at specific parts of the process where error can occur, or where errors can be minimised.

**Total Quality Management**

The total quality improvement perspective assumes that most providers are doing their best in the current system. Major improvements in system performance require redesign of systems rather than pushing people harder with the current system. Better systems should promote fewer errors and include effective mechanisms for catching those that do occur. They also cost less.

Bandolier is curious to know the equivalent ADE numbers in primary care.

Reference:


**Risk**

Bandolier 26 raised the question "should we have and use a "risk ladder" to help us, the public, and politicians understand the level of risk associated with a particular action or event". Recently, with BSE and other issues we have been told that risks are "very small" - but without attempting quantification.

Bandolier is therefore indebted to Dr Peter Iredale, Chairman of Oxfordshire Health and a member of Wolfson College for drawing our attention to a useful book based on the Wolfson lectures on risk held in 1984 [1]. The book, “Risk: man-made hazards to man”, with contributions from Hermann Bondi and Richard Southwood, is good reading. The chapter by William Inman (for many years connected with safety of medicines in the UK) on risks in medical interventions is compelling reading.

**Rules**

One useful quotation that Inman gives is from Lord Rothschild in his 1978 Dimbleby lecture. Rothschild said that when anyone makes a statement about an accident or the number of people involved in it, ask two simple questions:

1. Is the risk stated in a straightforward language that I can understand, such as 1 in 1,000? If not, why not?
2. Is the risk stated per year, per month, per day, or per some period of time? If not, I shall ignore the information.

**Scale of risk**

Inman also proposes and defines a risk ladder which can take into account the very wide confidence limits that should be put on any guesstimate of risk. This makes a logarithmic scale useful. The downside is that since risk has to start with certainty - 1 in 1 - this anchors the scale so that higher numbers on the risk scale represent lower orders of risk.
The scales would, for instance, put the risk of death for the UK population in any one year from any cause at 1 in 90 in risk level 2, with road traffic accident death (1 in about 14,000) in level 5, and being struck by lightning in level 8.

Of course the risk levels in the table are only crude and refer to the whole population of England & Wales. Risks can be modified by behaviour (there is a great quote in the book about keeping the working place safe so employees can go hang-gliding at the weekend), or by circumstance. The risk of dying in any one year is modified by age or by having or not having a particular disease.

In patients with specified diseases, the risks can increase, and Inman goes on to show how the use of the table of risk levels can be used to look at risks of treatments. There are some well reasoned pages about reactions to adverse drug events which are well worth a read.

**BSE**

Where does the BSE risk come on the scale? There were 4 or 5 cases of the “new” disease in humans in 1994 and 1995 - so the crude risk is about 1 in over 10,000,000 - just inside the level 8 band and about the same as being struck by lightning or winning the lottery. That crude risk is independent of causation, of course, as well as being the earliest indication of possible risk level that could change with time.

**Remember 3/n**

*Bandolier* 23 carried a short article on calculating the risk of something happening that we haven’t yet seen. If none of 100 patients receiving an intervention has a problem that concerns us, then we can be 95% confident that the chance of this occurring is at most 3 in 100 (3/n).

Reference:


Data taken from mortality statistics in England & Wales in 1981
CHLAMYDIAL STD TREATMENT

Bandolier was taken to task recently about the article in issue 26 on treatment of fungal nail infections. Along course of griseofulvin was compared with a short course of terbinafine, and the latter shown to be better. Our GP reader made the point that because terbinafine treatment was much shorter duration, possible adverse events were less likely; it was the treatment any sensible practitioner would prescribe for their grandmother so why was Bandolier suggesting the use of griseofulvin?

The point about simplicity of shorter duration antibiotic regimens is well made, exactly the point the Bandolier article was making, perhaps with insufficient force.

STD treatment guidelines 1993

The point about single dose oral therapy for sexually transmitted diseases (STD) was also made by a panel of experts from the Centres for Disease Control (CDC) in the USA, judging systematically amassed information. These guidelines [1] recommend a 1g single oral dose of azithromycin for chlamydial infections; the previously recommended regimen of oral doxycycline 100 mg twice daily for seven days remains an alternative treatment.

They mention that an important research issue is whether non-compliance with the 7-day doxycycline regimen results in treatment failures sufficiently high to warrant routine use of the more expensive single-dose azithromycin.

Bandolier thought that it would be worth looking at the evidence since chlamydia is the commonest curable cause of sexually transmitted disease in England & Wales. Data on new cases of infection from 1993 shows that men and women between the ages of 16 and 24 years are most often affected.

We did a simple search of MEDLINE from 1990 using azithromycin and chlamydia trachomatis as search terms. This was a sensitive strategy that brought up a number of papers, whose abstracts were examined to see if they were randomised trials or studies of cost-effectiveness.

Azithromycin and doxycycline compared

For randomised trials, the search was for studies which compared directly a 1g single oral dose of azithromycin with 100 mg oral doxycycline twice daily for seven days in chlamydial infections. The search identified nine trials with about 1,800 patients. Details of the trials are summarised in the table, with clinical or microbial cures reported at two weeks to allow comparison between the trials.

The main differences between trials were those that treated or included patients only with proven chlamydial infections, and those which treated all patients with appropriate symptoms. Two trials used a double-blind, double-dummy technique where patients took the same number of tablets or capsules over a week to maintain blinding. Numbers of patients analysed were often fewer than those enrolled, and analysis usually involved patients who tested positive for chlamydia and who attended follow up visits.

Results

Overall clinical cure rates were identical between the treatments at two weeks - 414 of 453 (91.4%) patients given azithromycin were cured, as were 293 of 316 (92.7%) of patients given doxycycline (odds ratio 0.91[95%CI 0.53 - 1.58]).

At two weeks there was no difference between the microbial cure rates - 279 of 301 (92.7%) patients given azithromycin compared with 243 of 253 (96.0%) of patients given doxycycline (odds ratio 0.53 [0.26 - 1.09]).

There was a trend for azithromycin cure rates to be higher than those of doxycycline at five weeks due to more frequent relapse in the latter group. Adverse events were mild and similar between treatments, though trials reported widely varying rates of adverse events. Reported events were 145 of 819 (17.7%) of patients given azithromycin compared with 243 of 253 (96.0%) of patients given doxycycline (odds ratio 0.53 [0.26 - 1.09]).

The most recent paper, that of Stamm et al [2], is the most detailed, and probably of the highest methodological quality, and worth reading, together with the accompanying editorial [3].

Efficacy and effectiveness

The editorial makes the point about patients in trials generally being compliant in taking their tablets, while “real-world” patients may not. This is the difference between efficacy (how well drugs work under ideal conditions) and effectiveness (how well drugs work under routine practice conditions). The authors of the editorial provide some interesting references about compliance, including a report that compliance with a 7-day treatment regimen in an STD clinic was only about 63%.
Summary of trials comparing single-dose azithromycin with one-week doxycycline

<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting</th>
<th>Design</th>
<th>Azithromycin cure</th>
<th>Doxycycline cure</th>
<th>Azithromycin adverse events</th>
<th>Doxycycline adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steingrimsson et al, J Antimicrob Chemother 1990, 25 Supp A: 109-114. (Iceland)</td>
<td>181 men and 1 woman attending STD clinic, in two phases with different antimicrobial regimens</td>
<td>random, blind, culture positive, attending follow-up for efficacy. Pfizer support</td>
<td>Microbial cure 55/61 (90%)</td>
<td>Microbial cure 54/58 (93%)</td>
<td>10/118 given azithromycin in any regimen</td>
<td>data not given</td>
</tr>
<tr>
<td>Whatley et al, Int J STD &amp; AIDS 1991, 2: 248-51. (UK)</td>
<td>62 men aged over 18 attending STD clinic.</td>
<td>random, open, 19 given azithromycin, 22 doxycycline. Pfizer support</td>
<td>Symptomatic and microbial cure 76.4%</td>
<td>Symptomatic and microbial cure 83.4%</td>
<td>no data</td>
<td>no data</td>
</tr>
<tr>
<td>Martin et al, N Engl J Med, 1992, 327: 921-5. (UK)</td>
<td>181 men and 1 woman attending STD clinic, in two phases with different antimicrobial regimens</td>
<td>random, open, multi-centre - 141 azithromycin, 125 doxycycline attended follow-up. Pfizer support</td>
<td>Clinical or microbial cure 109/111 (98%)</td>
<td>Clinical or microbial cure 96/96 (100%)</td>
<td>35 day survey all patients 41/237 (17%)</td>
<td>35 day survey all patients 43/220 (20%)</td>
</tr>
<tr>
<td>Nilsen et al, Genitourin Med 1992, 68: 325-7. (Norway)</td>
<td>130 men with clinical signs &amp; symptoms of urethritis, chlamydia antigen positive</td>
<td>random, double-blind, double-dummy, multicentre, attending follow-up. Pfizer support</td>
<td>Clinical cure 31/35 (99%) Microbial cure 35/35 (100%)</td>
<td>Clinical cure 32/34 (94%) Microbial cure 34/34 (100%)</td>
<td>35 day survey all patients 20/66 (30%)</td>
<td>35 day survey all patients 14/64 (22%)</td>
</tr>
<tr>
<td>Hammerschlag et al, Ped Pharmacol Ther 1993, 122: 961-5. (USA)</td>
<td>65 female and 8 male adolescents positive for chlamydia</td>
<td>random, open</td>
<td>Clinical cure 35/37 (95%)</td>
<td>Microbial cure 35/37 (95%)</td>
<td>35 day survey all patients 9/46 (20%)</td>
<td>35 day survey all patients 9/59 (16%)</td>
</tr>
<tr>
<td>Lauharanta et al, J Antimicrob Chemother 1993, 31 Supp E, 177-83. (Finland)</td>
<td>120 men with symptoms of non-gonococcal urethritis</td>
<td>random, open</td>
<td>Clinical cure 24/26 (92%) Clinical cure 19/20 (95%)</td>
<td>Microbial cure 26/26 (100%) Clinical cure 14/21 (67%)</td>
<td>35 day survey all patients 11/60 (18%)</td>
<td>35 day survey all patients 9/59 (16%)</td>
</tr>
<tr>
<td>Nilsen et al, Genitourin Med 1992, 68: 325-7. (Norway)</td>
<td>130 men with clinical signs &amp; symptoms of urethritis, chlamydia antigen positive</td>
<td>random, double-blind, double-dummy, multicentre, attending follow-up. Pfizer support</td>
<td>Clinical cure pos 12/16 (75%) Clinical cure neg 21/23 (91%)</td>
<td>Clinical cure pos 11/12 (92%) Clinical cure neg 30/30 (100%)</td>
<td>5/62 (8%)</td>
<td>9/66 (14%)</td>
</tr>
<tr>
<td>Steingrimsson et al, Sex Trans Dis 1994, 21:43-6. (Iceland)</td>
<td>183 men attending an STD clinic for symptoms or contact tracing</td>
<td>random, partial blind, microbial cure for three pathogens. Pfizer support</td>
<td>Microbial cure 130/142 (92%)</td>
<td>Microbial cure 111/117 (95%)</td>
<td>2/100 (2%)</td>
<td>2/83 (2%)</td>
</tr>
<tr>
<td>Stamm et al, JAMA 1995, 274: 545-9. (USA)</td>
<td>452 men with symptomatic non-gonococcal urethritis less than 14 days duration</td>
<td>random, double-blind, double-dummy. Pfizer support</td>
<td>Clinical cure 222/248 (90%) (95% CI 85-93%)</td>
<td>Clinical cure 110/123 (89%) (95% CI 82-94%)</td>
<td>23%</td>
<td>29%</td>
</tr>
</tbody>
</table>

Randomised trials comparing single dose Azithromycin with 7-day course of Doxycycline for Chlamydyal STD
Cost effectiveness

The CDC has also recently published a cost effectiveness study comparing single-dose azithromycin compared with a one-week course of doxycycline [4] in women. It was based on a four times higher cost of azithromycin, and a high (80%) compliance rate with doxycycline. It included scenarios of treating only chlamydia positive women, or presumptive treatment based on clinical signs and symptoms.

The results showed that from the perspective of the health care system, the higher medicine costs of azithromycin were offset by lower costs associated with pelvic inflammatory disease, chronic pelvic pain, ectopic pregnancy and tubal infertility. Treating chlamydia-positive women with azithromycin would save four times as much as the additional cost. Treating women only presumed to have chlamydial infection with azithromycin was broadly neutral in cost.

For both scenarios, compliance rates for doxycycline which fell below 80%, or lower medicine costs of azithromycin compared with doxycycline made the azithromycin choice even more cost effective.

References:
2 Suppl;S96-S101.

Perhaps it is indicative of the difficulties that exist in this area that this has easily been the single most contentious issue ever run in Bandolier.

A number of correspondents have asked why we did not mention the use of likelihood ratios for diagnostic tests - suggested for some time as a more effective way of using diagnostic tests. Since this is a mea culpa time, the answer is simple - Bandolier forgot! Interesting, though, was how few of an audience of producers of diagnostic test results, and of users, knew about it. So, with its heart in its mouth, Bandolier has another go.

Data

Let’s use the data on smoking and smoking tests mentioned in Bandolier27 [1]. The researchers examined a general practice data base in Belfast, and examined 591 patients with a history of coronary heart disease; 153 were self-reported smokers. They were part of a randomised trial of smoking cessation.
Four biochemical tests of smoking status were used, the best of which were urinary measurements of nicotine metabolite (with or without creatinine correction). They also identified a small group of ‘smoking deceivers’ - people who said they did not smoke, but who had urine nicotine metabolite concentrations typical of those of smokers.

Sensitivity and specificity are given in the table for all results and for results excluding smoking deceivers.

**Likelihood ratio**

The likelihood ratio (LR) can be calculated from the sensitivity and specificity of a test expressed as ratios rather than percentages. It expresses the odds that a given finding would occur in a patient with, as opposed to without, the target disorder or condition. It is derived as:

\[
\text{LR}_{\text{pos}} = \frac{\text{sensitivity}}{1 - \text{specificity}}
\]

With the LR above 1, the probability of the disease or condition being present goes up; when it is below 1 the probability of it being present goes down, and when it is exactly 1 the probability is unchanged.

LR can also be calculated for the negative, as well as the positive. To find the odds that a given finding would not occur in a patient without, as opposed to with, the target disorder or condition, LR is derived as:

\[
\text{LR}_{\text{neg}} = \frac{1 - \text{sensitivity}}{\text{specificity}}
\]

**Using the LR for tests of smoking status**

Positive and negative LRs are calculated in the table. They are used by reference to the nomogram. The pre-test probability is a simple calculation - it is what proportion of this population is known to smoke before any tests are done; it is 153/591, or about 25%.

Using that as the starting point, the LRs can be used to give the post-test probability that any patient is a smoker when the result of the test is known. Three lines have been put on the nomogram for three possible circumstances:

A: if the test is positive, using all results for either test gives a post-test probability of a patient being a smoker of about 85%.

B: if the test is positive and we are happy to use data with smoking deceivers excluded (which seems reasonable), then a positive urinary nicotine metabolite test has an LR of 98, and we can be about 97% sure the patient is smoker.

C: for any negative test, LRs are very low and we can be more than 99% sure that the patient does not smoke.

### Some comments

Likelihood ratios are useful in several ways. Firstly they seem comprehensible and can be used to support or exclude a diagnosis. They can also be used sequentially so that the post-test probability after one diagnostic test can be used as a pre-test probability for the next. LRs can also be calculated at several levels of a test which produces numerical data.
The other thing that the nomogram indicates is just how good tests need to be to be useful in screening. Screening is usually done when the pre-test probability is low - often less than 1%. Here even a good test gives a low post-test probability. Just for fun, use the nomogram with a few examples you make up.

Of course, one needs some information on the sensitivity and specificity of tests, or LRs, and pre-test probabilities. If readers think this approach is useful, then Bandolier will try and find some examples.

Postscript

Just in case anyone was wondering what happened in the trial of smoking cessation in Belfast, there was no evidence that a health visitor encounter every 4 months for 2 years made much difference.

Useful references:

Evidence-based friendliness?

Friendly dentists

A famous but little-known trial is the Friendly Dentists Trial, the reference for which has disappeared down a Bandolier cavity. In this trial two types of dental practice were offered to people who required dentures. In one the dentists discussed options with patients, involved them in decision making and shared both the responsibility and the pleasure of a satisfactory outcome. The other arm of the trial was said to be conventional dental practice (this was a North American trial). The outcome of the trial demonstrated clearly that the friendly dentist got better clinical outcomes than the conventional dentist.

Friendly physicians

Evidence of the effectiveness of friendliness was produced by a cross-sectional survey of 7,730 from the practices of 300 physicians [1]. This study, part of the justly famous Medical Outcomes Study, found that:

“The patients whose physicians were rated the least participatory were most likely to change physician.

The greater the level of participation the greater degree of patient satisfaction.

Physicians who had primary care training or training in interviewing scored higher than those without such training.

Physicians in higher volume practices were rated as less participatory than those in lower volume practices.

Physicians who were satisfied with the level of professional autonomy were rated as more participatory than those who were dissatisfied.”

The authors raise the fascinating possibility that “because participatory decision making style is related to patient satisfaction and loyalty to the physician, cost containment strategies that reduce time with patients and decrease physician autonomy may result in sub-optimal patient outcomes.”

Better for business

It is a different system from ours. The questionnaire used was one developed in North America so the results cannot simply be taken at face value until related to Britain, but there appears to be very strong evidence that the participatory friendly style of practice is better for patient care and, if patients can vote with their feet, for business.

Longer consultations are cost-effective

The message is clear: longer, more participatory and friendly consultations are cost-effective in the long term although the costs may be greater in the short term.

The article concludes by arguing that improving interviewing skills improved both the physician’s and the patient’s satisfaction with care. Improving the quality of the consultations that professionals do about 200,000 or 300,000 times in their lifetime makes physicians both feel and do better. Thus the development of better interviewing skills should not be seen simply as an altruistic device to improve patient satisfaction but as part of a self-interested campaign for physician survival.

Reference: