This month we have just two stories. We revisit some methodological issues not out of some arcane Reithian motive but because many readers have asked for a summary of the approach we use. So Bandolier examines L’Abbé plots and numbers-needed-to-treat or to harm which we find so useful as indicators of clinical utility. A Bandolier review of proton pump inhibitors and H2-antagonists in gastro-oesophageal reflux disease (GORD) is used as an example of ways to calculate NNTs. The review is published in full on Bandolier’s Internet pages, and we would welcome comments.

**Mystery writer**

*Bandolier* is pleased to tell the world that the mystery writer on shop floor epidemiology in issue 34 was Paul Aveyard from the Department of Public Health & Epidemiology at the University of Birmingham.

**19th century revival**

Letter writing is not as fashionable as it once was. It is hard to imagine the fascinating correspondence between Florence Nightingale and Benjamin Jowett being conducted over the telephone. *Bandolier* feels that the art may be reviving, because you are filling our post-box. We have but eight paper pages, so correspondence is posted on our Internet pages. This disenfranchises the electronically challenged, so a brief summary of current pen rage items follows.

**Brittas Empire**

Warts, verrucas and minor surgery have provoked letters from many surgeries. One current bone of contention is whether protective clothing should be worn by the uninfected when they visit the leisure centre - “Brittas demands bilateral condoms”. It is good to see that proce-

Continued on page 8...

### Getting NNTs

Systematic reviews of randomised controlled trials provide the highest level of evidence of efficacy of treatments - though in other circumstances, such as adverse events or diagnostic tests, randomised trials may not always provide the best evidence. Commonly accepted levels of efficacy evidence were shown in *Bandolier* 12, and are worth revisiting, so it appears on page 8.

#### Output from systematic reviews

The evidence provided in systematic reviews can take various forms. Often it is statistical - an odds ratio, relative risk, hazard ratio or effect size. These show statistical superiority of one treatment over another, or over no treatment, but they are a bit difficult when we try and relate them to clinical practice. *Bandolier* has favoured the number-needed-to-treat [1] as a useful way of looking at results of reviews or trials for at least two reasons. It is easy to calculate, and provides the treatment-specific result in a form which we can handle. Using NNTs is a bit trickier. *Bandolier* has started thinking of the NNT in two ways.

#### Black bag evidence

Firstly - and this is where most systematic reviews are useful - it can help us to make decisions between treatment options. If the NNT for treatment A is lower (better) than treatment B, then, all other things being equal, choosing A over B makes sense. Here the choice is what to put in the black bag. A would go into the black bag, B would not.

The other way to use an NNT is when you make choices for an individual patient, perhaps whether to treat or not. The choice here is whether or not to take A out of the black bag and use it.

There are, of course, many nuances to all this. *Bandolier* recommends a new book from David Sackett & colleagues - *Evidence-based Medicine: how to practice and teach EBM* - as a cheap and worthwhile acquisition for any thinking doctor, nurse, scientist or manager in the NHS [2].

Readers who find NNTs helpful, but who are not entirely comfortable with them, have asked *Bandolier* to work through some examples of how to obtain and use NNTs. To do this from existing reviews can be difficult, since not all the information is to hand. So *Bandolier* has done its own systematic review comparing proton pump inhibitors (PPIs) and H2-antagonists (H2As) in the short-term healing and long-term maintenance of reflux oesophagitis. The full text of the review and associated tables and graphs is available on the *Bandolier* Internet pages. The information from that review will be used to show how NNTs can be calculated in different ways. NNTs can be calculated from raw data using a formula, from odds ratios, or from relative risk reduction and expected prevalence.
NNT can be calculated from

1 - raw data (use Formula)
2 - published odds ratios (use Table)
3 - relative risk reduction and prevalence (use Nomogram)

1 Calculating NNTs

The NNT calculation is given below. We need to distinguish between treatments, such as aspirin as an analgesic, and preventative measures, such as aspirin preventing further cardiac problems after myocardial infarction. Using the number outputs from systematic reviews is different depending on which you are looking at. The distinction is between treatment and prophylaxis. For prophylaxis, where fewer events occur in the treated group, the calculation shown will produce negative NNTs. You can use those (the number will be correct), or you can switch the active and control groups around to provide NNTs with a positive sign.

The NNT for prophylaxis is given by the equation \( \frac{1}{(\text{proportion benefiting from control intervention} - \text{proportion benefiting from experimental intervention})} \), and for treatment by \( \frac{1}{(\text{proportion benefiting from experimental intervention} - \text{proportion benefiting from control intervention})} \).

NNTs for treatment should be small. We expect large effects in small numbers of people. Because few treatments are 100% effective and because few controls - even placebo or no treatment - are without some effect, NNTs for effective treatments are usually in the range of 2 - 4. Exceptions might be antibiotics. The NNT for Helicobacter pylori eradication with triple or dual therapy, for instance, is 1.2 (Bandolier 12).

NNTs for prophylaxis will be larger, few patients affected in large populations. So the difference between treatment and control will be small, giving large NNTs. For instance, use of aspirin to prevent one death at five weeks after myocardial infarction had an NNT of 40 (Bandolier 17).

Using absolute risk reduction

The absolute risk reduction (ARR) is the difference between the event rate in the experimental group and the event rate in the control group. It is the denominator in the NNT calculation. Many reviews and trials provide this information, so if you have it and convert it into a proportion, then you can get the NNT by dividing 1 by the ARR:

\[ \text{NNT} = \frac{1}{\text{ARR}} \]

Confidence Intervals

The 95% confidence intervals of the NNT are an indication that 19 times out of 20 the ‘true’ value will be in the specified range. An NNT with an infinite confidence interval is then but a point estimate; it includes the possibility of no benefit or harm. It may still have clinical importance as a benchmark until further data permits finite confidence intervals, but decisions must take this into account. A method for calculating confidence intervals was given in Bandolier 18.

\[
NNT = \frac{1}{(\text{IMP}_{act}/\text{TOT}_{act}) - (\text{IMP}_{con}/\text{TOT}_{con})}
\]

where:

- \( \text{IMP}_{act} \) = number of patients given active treatment achieving the target
- \( \text{TOT}_{act} \) = total number of patients given the active treatment
- \( \text{IMP}_{con} \) = number of patients given a control treatment achieving the target
- \( \text{TOT}_{con} \) = total number of patients given the control treatment
2 Using odds ratios

When it is legitimate and feasible to combine data the odds ratio is the accepted statistical test to show that the experimental intervention works significantly better than control. If a quantitative systematic review produces odds ratios but no NNTs, you can derive NNTs from the table provided [3].

A caveat here is that odds ratios should be interpreted with caution when events occur commonly, as in treatments, and odds ratios may over-estimate the benefits of an effect when event rates are above 10%. Odds ratios are likely to be superseded by relative risk reduction because relative risk reduction provides better information in situations where event rates are high [3, 4].

### Odds Ratios (OR)

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</table>

Odds ratios are on the top line and control event rates (CER) down the left hand side. NNTs are in the boxes. So if you have an odds ratio (eg 0.6) and a CER (eg 0.5), then the NNT will be found where they cross (NNT = 8).

3 Relative risk reduction

Chatelier and colleagues published a useful NNT nomogram in the BMJ last year [5]. Relative risk reduction - the percentage reduction in risk between the experimental and control group - is used to calculate the NNT for any group in whom the risk of an event happening was known.

This is probably most likely to be used in prophylaxis. If you have a review or paper which gives a RRR (in percent) and you know the susceptibility of your patient for a bad outcome (usually called the ‘patient expected event rate’, or PEER), then you can find out the NNT of an intervention.

RRR is calculated by dividing the difference between the rate of events in experimental and control group by the rate of events in the control group. So if 10% of patients have a bad event in controls, and only 9% with some intervention, the RRR is (10-9)/10 = 10%. Relative risk reductions happen in prophylaxis. With treatments we have relative risk increase because we expect more good events. The method works either way.

Say the RRR is 50%, and the PEER is 50%. Then the NNT from the nomogram is 4. But if the RRR is 10% and PEER is 10% then the NNT is about 90.
L’Abbé plots

A paper [6] by Kristen L’Abbé and colleagues written ten years ago is regarded by Bandolier as one of the most sensible and understandable ever written on systematic reviews. The authors suggest a simple graphical representation of the information from trials. Each point on a L’Abbé scatter plot is one trial in the review. The proportion of patients achieving the outcome with the experimental intervention is plotted against the event rate in controls. Even if a review does not show the data in this way, you can do it yourself if the information is in the review.

For treatment, trials in which the experimental intervention was better than the control will be in the upper left of the plot, between the y axis and the line of equality. If experimental was no better than control then the point will fall on the line of equality, and if control was better than experimental then the point will be in the lower right of the plot, between the x axis and the line of equality.

For prophylaxis this pattern will be reversed. Because prophylaxis reduces the number of bad events - such as death after myocardial infarction by the use of aspirin - we expect a smaller proportion harmed with treatment than with control. So if experimental is better than control the trial results cloud should be between the x axis and the line of equality.

These plots give a quick indication of the level of agreement among trials. If the points are in a consistent cloud, that gives some confidence that what we are seeing is a homogenous effect. But if points are spread all over the graph, and especially if they cross the line of equality, then that should make us concerned about the intervention, or the patients being treated and their condition. This can also be called heterogeneity.

The important point about a L’Abbé plot is that it shows all of the extant data on one piece of paper. When combined with numbers in the trial, and a summary measure like NNT, it is a neat way to summarise lots of information.

[Diagram of L’Abbé plot for treatment]

Using NNTs

Variation in treatment and control

One of the things that plotting information from systematic reviews in L’Abbé plots teaches you is just how variable are the effects of both treatment and control in randomised trials. It is legitimate to be surprised, but after quite a short time it seems that this is the norm.

The reasons are probably complex, but much of the variability will be just random chance. In many circumstances patients can have quite wide patterns of response to a treatment, but trial size for treatments is often relatively small, because trials are hard to do. Gathering data together in systematic review and meta-analysis gives much more power than the single trial in almost all circumstances, and especially for reviews of treatments. Seeing such variability also teaches caution when you are faced with a single trial with apparently excellent (or hopeless) results.

Comment

There will be circumstances where systematic reviews will not yield information to generate L’Abbé plots, NNTs, relative risk, or even odds ratios. There are times when the information for quantitative systematic review is just not available. Where they are available, then we can use information in our practice.

Using NNTs for particular patients

The choice of what goes into the black bag will also reflect the choice of what comes out of it. Simplistically, if we are convinced by the evidence shown from page 5 on that omeprazole is better than ranitidine for healing reflux oesophagitis, then we might use omeprazole, though there will be arguments over the value of stepped treatment.

Bandolier will use the example of dog-bite infection (the subject of a recent BMJ editorial [7] and a previous Bandolier review in issue 16) as an example of how NNTs can be used to make judgements on a specific patient.

Dog bite infection

Suppose a woman presents with a dog bite. Her immune system is compromised by steroid therapy for asthma. Should we give prophylactic antibiotics to prevent infection? We know from a quantitative systematic review of RCTs [8] that there is evidence for benefit with an overall NNT of 16. How can we apply this to our patient?

She is immunocompromised, so her risk of becoming infected is many times higher than the non-compromised patients in the review. We estimate her increased risk (usually called F), to be 5 times greater than the 16% average rate of infection in the review (though in individual studies risk varied between 3% and 46%). Assuming a constant relative risk, the estimated NNT corresponding to an F of 5 is then NNT/F = 16/5 = 3 [2].
So while prophylactic antibiotic treatment of dog bite to prevent infection may not be worthwhile for all patients (NNT of 16), it may well be so for our particular patient (NNT of 3).

Suppose we live in Middlesborough? We know from an RCT that infection rates there are about 50%, so we might be likely to treat all patients. For patients in Middlesborough, the “patient expected event rate”, or PEER, is 0.5 compared to the 0.16 average found in the review. The review gave us an odds ratio of 0.6 for prophylactic antibiotics.

If we look down the line of 0.6 in the Table of odds ratios and NNTs, stop at a control event rate (our PEER) of 0.5, we find an NNT of about 8. Now if half our patients bitten by a dog are going to get an infected wound, and by using antibiotics we can stop that happening just once in every eight times, then we save six patients in every 100 having an infected bite.

So even in Middlesborough our prophylactic antibiotics won’t stop every infection, but perhaps enough to make it worthwhile. Perhaps changes in practice and knowledge will make it more likely that we want to intervene in this way [7].

**NNTs to inform patients?**

This is a difficult area. Because an NNT is treatment-specific, it will not include all the power of an intervention - a placebo response, for instance. Patients want to know their chance of getting better or being harmed, and that includes influences from all sources. The best analogesics have NNTs of 2 for at least 50% pain relief (a high hurdle), which implies that half the patients will achieve at least 50% pain relief because of the analgesic. But the placebo effect will add perhaps another 20% to this, so that reality is that 70% achieve at least 50% pain relief with the analgesic, which sounds better and reflects the reality.

But that is a simple example. Most circumstances are more complex. The LBBH (likelihood of being helped or harmed) has been suggested as one way of presenting information to patients [9], but there is a clear need for more empirical research to provide evidence on how best to do this.


**Reflux Oesophagitis**

A review of all proton pump inhibitors compared with all histamine antagonists is published on the Bandolier Internet pages (http://www.jr2.ox.ac.uk/Bandolier/bandopubs/gordf/gord.html). It was supported by an educational grant from the Astra Foundation. Editorial control was solely that of the authors. Data from direct comparisons of omeprazole and ranitidine only have been used here as an example of deriving NNTs from different types of output.

Gastro-oesophageal reflux is the process of reflux of stomach contents into the oesophagus. The consequence is a chemical insult from acid and enzymes. Reflux happens commonly but infrequently in many people, and it does not cause major harm because the natural peristalsis of the oesophagus clears the refluxate back into the stomach. In others where acid reflux from the stomach is persistent, the result is damage to the oesophagus causing symptoms or macroscopic oesophageal damage, and here gastro-oesophageal reflux disease (GORD) can be said to be present.

GORD produces a characteristic set of symptoms, though significant oesophagitis can be present without symptoms. Heartburn is most common; it is often described as gnawing or burning pain behind the sternum, and it may be severe enough to radiate to the arm or jaw. Usually occurring within an hour or so of a meal it can be made worse by lying down. Heartburn can wake the patient at night, and is most frequent in those with the most severe disease. Heartburn occurs occasionally in many people after a fatty or spicy meal, but in GORD the symptoms occur frequently after any sort of meal. Alcohol and coffee also induce symptoms. Antacids relieve symptoms.

**Oesophageal damage**

The lining of the oesophagus is ill-equipped to resist stomach acids. The stomach has cells which produce a bicarbonate-mucus barrier which protects them from stomach acid: oesophagus does not have this protective barrier. The result of refluxed stomach acid is to damage the lining of the oesophagus. This damage can be microscopic, but is often macroscopic and seen on endoscopy.

Endoscopic oesophageal damage is graded on a scale of 1-4 with increasing severity of damage.

- **Grade 0** is given to normal oesophagus with no macroscopic damage.
- **Grade 1** describes an oesophagus with a few areas of erythema, mucosal friability and contact bleeding. These are minor changes regarded as normal by some gastroenterologists.
- **Grade 2** oesophagitis has small superficial linear erosions. These tend to lie on the crests or tops of the mucosal folds and may have some surface exudate.
- **Grade 3** describes the condition when these erosions coalesce and join around the circumference of the oesophagus. A cobblestone appearance is created by islands of oedematous tissue between the erosions.
- **Grade 4** is characterised by extensive mucosal damage with deep ulcers. Strictures may develop, and where this
happens there may be less damage above the stricture because the stricture forms a barrier to stomach acids.

The correlation between endoscopic grading and symptoms is not good. Severe symptoms can occur with low grade oesophagitis, and conversely severe oesophageal damage can sometimes occur with few symptoms.

### Prevalence

Surveys in the USA have indicated that 44% of the adult population has heartburn at least once a month. Six out of ten of these never consult a GP about it. About 13% of the adult population take some type of indigestion aid at least twice a week. There seem to be few reliable figures on the numbers of patients who present to GPs with reflux symptoms, but a health authority with an adult population of 470,000 will have an estimated 7,500 patients seeing GPs with dyspepsia and almost 3,000 having an endoscopy, over half for oesophageal or gastrointestinal problems, including suspected ulcer.

### Treatment options

These include lifestyle change and use of antacid or alginates; none of these is particularly effective. Mucoprotective agents and motility stimulants may be used, but suppression of acid secretion with H2A or PPI is the most common form of treatment. Antireflux surgery is said to be useful in some patients, and to be effective.

### Systematic review

Reports were sought of comparisons between any proton pump inhibitor (PPI) and any histamine-2 antagonist (H2A) in reflux oesophageal disease with endoscopic healing as the outcome measure. Both short-term healing and long-term maintenance were included. Papers were included in the systematic review of effectiveness if they fulfilled the criteria:

- Full journal publication
- Randomised trial
- Compared PPI with H2A, or
- Compared either PPI or H2A with placebo
- Examined gastro-oesophageal reflux disease (GORD), erosive oesophagitis or gastritis, or reflux oesophagitis
- Had endoscopic healing as an outcome or
- Had adverse event outcomes
- Had short-term outcomes at 4 and/or 8 weeks, or
- Had long-term maintenance outcomes at 6 or 12 months

### Short-term healing

Twenty-three reports with 5,118 patients fulfilled the inclusion criteria. One report had no endoscopic healing data, but did have adverse event information. Of the reports with endoscopic healing, ten (1393 patients) compared omeprazole with ranitidine, two reports (339 patients) omeprazole with cimetidine and three reports (525 patients) lanzoprazole with ranitidine. Quality scores were high using a validated scale from 1 to 5 [1]. Four studies had a score of 2, three of 3, eleven of 4 and five of 5. The median score was 4. Bandolier 33 showed how it is important to use studies of high quality (scores above 2) to avoid over-estimating treatment effects.

Information from randomised controlled trials which compared ranitidine and omeprazole with endoscopic healing of erosive oesophagitis after eight weeks is shown in the Table below. The overall NNT for omeprazole compared with ranitidine was 3.3. This mean that for every three patients with erosive reflux oesophagitis treated with omeprazole, one will be healed who would not have been healed if they had been treated with ranitidine.

Odds ratios, relative risk and NNTs have been calculated, and the rate of healing in the omeprazole and ranitidine groups is shown in the Table for each trial.

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<tr>
<th>Trial</th>
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Summary data from randomised controlled trials comparing omeprazole and ranitidine for endoscopic healing of erosive oesophagitis after eight weeks. EER is 8-week endoscopic healing rate with omeprazole and CER the 8-week endoscopic healing rate with ranitidine.
NNT from RRR

The relative risk increase from the table is \((78-44)/44 = 77\%\). The PEER is 44\%, and our NNT from the nomogram is 3.

Long-term maintenance

Seven reports with 1,635 patients fulfilled the inclusion criteria. Four reports (1094 patients) compared omeprazole with ranitidine, one omeprazole with placebo, one lansoprazole with placebo and one omeprazole and ranitidine alone and in combination with cisapride. The most commonly used doses were omeprazole 20 mg and ranitidine 300 mg daily. Two studies had a quality score of 3, four of 4 and one of 5.

Information from randomised controlled trials which compared ranitidine and omeprazole with endoscopic healing of erosive oesophagitis after eight weeks is shown in the Table on page 8. The overall NNT for omeprazole compared with ranitidine was 2.8. This mean that for every three patients with healed erosive reflux oesophagitis treated with omeprazole, one more will still be healed after one year who would not have been if they had been treated with ranitidine.

L’Abbé plot

This shows that all the studies are well to the upper left of the line of equality meaning that in all trials omeprazole was more effective than ranitidine. The L’Abbé plot also provides extra information that the NNT does not. While the NNT gives us the \textit{treatment-specific} benefit of omeprazole over ranitidine, the L’Abbé plot shows us the overall effect of treatment. So we can see that about 80\% of patients are healed with omeprazole while only about 45\% are healed with ranitidine.

NNT from ARR

For the overall results, the proportion getting benefit with omeprazole was 78\%, or 0.78, and for ranitidine it was 44\% or 0.44. So the NNT calculation becomes:

\[
\text{NNT} = 1/\text{ARR} = 1/(0.78-0.44) = 1/0.34 = 3
\]

which is close to the 3.33 calculated from raw data in the review.

NNT from OR

Looking at the table of odds ratios and NNTs later in this issue, if we go to the column with the odds ratio nearest the overall of 3.7, and track along the control event rate nearest that in our review for ranitidine of 0.4, we obtain an NNT of 3. Again close to the overall NNT of 3 calculated from raw data in the review.

NNT from ARR

For the overall results, the proportion getting benefit with omeprazole was 70\%, or 0.70, and for ranitidine it was 30\% or 0.30. So the NNT calculation becomes:
NNT = 1/ARR = 1/(0.70-0.30) = 1/0.40 = 2.5

which is close to the 2.8 calculated from raw data in the review.

NNT from OR

Looking at the table of odds ratios and NNTs later in this issue, if we go to the column with the odds ratio nearest the overall of 4.2, and track along the control event rate nearest that in our review for ranitidine of 0.3, we obtain an NNT of 3. Again close to the overall NNT of 2.8 calculated from raw data in the review.


<table>
<thead>
<tr>
<th>Trial</th>
<th>Odds Ratio</th>
<th>Relative Risk</th>
<th>NNT</th>
<th>Total in trial</th>
<th>EER</th>
<th>CER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lundell Om 20 vs Ran 300</td>
<td>5.67</td>
<td>5.50</td>
<td>2.44</td>
<td>68</td>
<td>50</td>
<td>9</td>
</tr>
<tr>
<td>Smith Om 20 vs Ran 300</td>
<td>5.02</td>
<td>2.84</td>
<td>2.50</td>
<td>257</td>
<td>61</td>
<td>21</td>
</tr>
<tr>
<td>Dent Om 20 vs Ran 300</td>
<td>12.96</td>
<td>3.48</td>
<td>1.59</td>
<td>104</td>
<td>89</td>
<td>25</td>
</tr>
<tr>
<td>Hallerback Om 20 vs Ran 300</td>
<td>2.96</td>
<td>1.58</td>
<td>3.85</td>
<td>259</td>
<td>72</td>
<td>45</td>
</tr>
<tr>
<td>Vigneri Om 20 vs Ran 450</td>
<td>3.85</td>
<td>1.65</td>
<td>3.23</td>
<td>70</td>
<td>80</td>
<td>49</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>4.23</strong></td>
<td><strong>2.11</strong></td>
<td><strong>2.78</strong></td>
<td><strong>758</strong></td>
<td><strong>70</strong></td>
<td><strong>30</strong></td>
</tr>
</tbody>
</table>

Summary data from randomised controlled trials comparing omeprazole and ranitidine for maintenance of endoscopic healed erosive oesophagitis after time point nearest to one year. EER is one-year still-healed rate (on endoscopy) with omeprazole and CER the one-year still-healed rate (on endoscopy) with ranitidine.

Go faster nose strips bite the dust

Readers from Devizes, Newcastle, Bristol and Chesterfield gave Bandolier the evidence that nose strips do not increase athletic prowess. Citations to the trials are posted on the web. As our correspondents pointed out it would be unusual to find a top rugby player who could breathe through their nose (at rest). Bandolier declares the strips to be decorative and part of the dressing room ritual of unguents and incantations (male bonding). More on the fetishism of outdoor games on the letters page ...

Skeins of geese

The indoor games editor thanks correspondents for their kind replies. Without exception they concentrated on the reason the birds change places - because there is greater wind resistance etc. at the apex of the V. IGE respectfully submits that the core question - the decision-making which precedes the change-over, is unexplained. Does the lead bird tire and decide to move back in the skein or do others notice a fall-off in stroke rate and that prompts the move?