

Understanding measures of treatment effect in clinical trials

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Evidence based medicine implies that healthcare professionals are expected to base their practice on the best available evidence. This means that we should acquire the necessary skills for appraising the medical literature, including the ability to understand and interpret the results of published articles. This article discusses in a simple, practical, 'non-statistician' fashion some of the important outcome measures used to report clinical trials comparing different treatments or interventions. Absolute and relative risk measures are explained, and their merits and demerits discussed. The article aims to encourage healthcare professionals to appreciate the use and misuse of these outcome measures and to empower them to calculate these measures themselves when, as is frequently the case, the authors of some original articles fail to present their results in a more clinically friendly format.

admitted with RSV infection was 10.6% for those receiving placebo and 4.8% for those receiving prophylactic palivizumab. It should be noted that AR and all the other measures of treatment effect discussed below are statistical estimates and the uncertainty in the estimates should be accompanied by confidence intervals.

Absolute risk reduction

In a study comparing a group of patients who were exposed to a particular intervention with another group who did not receive the intervention, the absolute risk reduction (ARR) is calculated as the arithmetic difference in the AR of an outcome in individuals who were exposed to the intervention and the AR of the outcome in those unexposed to the intervention. From the data in table 1, the absolute risk reduction with regard to RSV hospitalisation for children who received palivizumab compared with those who received placebo is calculated as (10.6%–4.8%) or 5.8%. This risk difference reflects the additional risk of being admitted to hospital for children receiving placebo compared with those receiving palivizumab. In other words, receiving palivizumab reduced an infant's risk of being admitted with RSV infection by 5.8%.

Number needed to treat

Absolute risk measures are of immense importance in clinical practice because the reciprocal of the ARR is equivalent to the number needed to treat (NNT), which is a more user friendly way of reporting outcomes. NNT is defined as the number of people who need to receive the intervention in order to achieve the required outcome in one of them. NNT represents a clinically useful way of describing risk as it is much easier to conceptualise. As stated earlier, the NNT is calculated simply as the reciprocal of the ARR. Earlier, I used the data from table 1 to calculate the absolute risk reduction with regard to RSV hospitalisation for children who received palivizumab compared with those who received placebo as 5.8% or 0.058. The NNT is 1/0.058 or 17.2. This means that about 17 high risk infants needed to receive the stated dose of palivizumab in order to prevent one of them from being admitted to hospital with an RSV infection during the 150 day period.

In clinical trials comparing different interventions, outcomes can be measured in a variety of ways. Not all of these outcome measures depict the significance or otherwise of the intervention being studied in a clinically useful way. I will describe these important measures and illustrate their meanings and the relation between them using data from table 1.

These data are adapted from a multicentre double blind, randomised, placebo controlled trial that investigated the efficacy of prophylaxis with the humanised respiratory syncytial virus (RSV) monoclonal antibody, palivizumab, in reducing the incidence of hospitalisations due to RSV infections in high risk infants.¹ A total of 1502 children with prematurity (≤ 35 weeks) or bronchopulmonary dysplasia (BPD) were randomised to receive five intramuscular injections of either palivizumab (15 mg/kg) or an equivalent volume of placebo every 30 days during an RSV season. The children were followed up for a total of 150 days.

ABSOLUTE RISK MEASURES

Absolute risk

Absolute risk (AR) refers to the chance of an occurrence—that is, the probability of an outcome occurring.² From the data in table 1, the AR of being admitted to hospital for children receiving placebo is $53/500 = 0.106$ or 10.6%. For children receiving palivizumab, the absolute risk is $48/1002 = 0.048$ or 4.8%. This means that the chance or the probability of an infant being

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Table 1 Number of children admitted to hospital with RSV infection following placebo or prophylactic palivizumab¹

	Admitted	Not admitted	Total
Placebo	53	447	500
Palivizumab	48	954	1002
Total	101	1401	1502

RELATIVE RISK MEASURES

Relative risk

Relative risk (RR) puts risk in comparative terms, and indicates the ratio of the risk of an outcome in the exposed group to the risk of the outcome in the unexposed group.² If the risks in the two groups are the same, then the relative risk will be equal to one. From table 1, the RR of being hospitalised for those receiving prophylactic palivizumab compared to those receiving placebo is $4.8/10.6 = 0.45$. This means that the probability of being admitted to hospital for those receiving prophylactic palivizumab was 0.45 times or about half of that of those receiving placebo.

Relative risk reduction

Relative risk reduction (RRR) measures how much the risk is reduced in the treatment group compared with the control group. Using the data in table 1, the RRR is calculated as $(10.6 - 4.8)/10.6 = 55\%$. This means that the chance of a high risk infant being admitted to hospital is reduced by 55% in the palivizumab group compared with the placebo group. RRR can also be calculated by simply subtracting the relative risk from one ($1 - RR$). In our example, the RRR can be calculated as $(1 - 0.45)$ or 0.55 or 55%.

Advantages and disadvantages of risk measures

Both absolute risk and relative risk measures have their advantages and disadvantages. Relative risk measures have the advantage of being stable across populations with different baseline risks and are, for instance, useful when combining the results of different trials in a meta-analysis. However, they have the major disadvantage of not reflecting the baseline risk of the individuals with regard to the outcome being measured. That is, relative risk measures do not take into account the individuals' risk of achieving the intended outcome without the intervention. Therefore, they do not give a true reflection of how much benefit the individual would derive from the intervention, as they cannot discriminate between small and large treatment effects. They usually tend to overestimate the benefits of an intervention and, for this reason, drug companies and the popular media love relative risk measures! Absolute risk measures overcome these drawbacks because they reflect the baseline risk and are better at discriminating between small and large treatment effects.³

Using the data from table 1, you will recall that I calculated the ARR as 5.8% and the relative risk reduction as 55%. Fifty five per cent reduction in risk *feels* more impressive than 5.8%, and a drug company representative promoting palivizumab may prefer to quote the 55% RRR. This figure is also highlighted in the article by the IMpact-RSV study group.¹ The clinical significance of these percentages is difficult to conceptualise, but the results could be presented in a more user friendly way by converting the ARR to NNT which was calculated to be 17. Although the NNT is a clinically useful measure of treatment effect which clinicians may find easier to understand, the ability of patients to easily grasp the concept is controversial.⁴

A HYPOTHETICAL EXAMPLE

To further understand the differences between absolute and relative risk measures, consider a hypothetical situation where, for those who have disease Y, the risk of dying from it over a five year period without treatment (baseline risk) is 0.005%, and the risk of dying from the same disease when you are treated with drug X is 0.001%. The drug company representative could come to you and say that the risk of dying from disease Y is reduced by 80% when you take drug X. Most people will jump at the chance of taking a drug that will reduce their risk of dying by 80%! Technically, the drug company is right as they are quoting the relative risk reduction $(0.004/0.005 \times 100)$. However, because the baseline risk of dying (0.005%) is so trivial, the 80% reduction in risk to 0.001% is also trivial and is unlikely to be of much clinical benefit to the patient. What the drug company representative may not tell you is that the absolute risk reduction is 0.005%–0.001% or 0.004% because compared to “reduced the risk by 80%”, the alternative statement “reduced the risk by 0.004%” immediately gives the feel of a trivial effect.

In this hypothetical example, the NNT is calculated to be $100/0.004$ or 25 000. This means that you will need to treat 25 000 disease Y patients with drug X in order to prevent one of them from dying from the disease over the stated five year period. Thus the NNT would be much more beneficial in conveying the “truth” here as they are likely to immediately tell you that the reduction in the risk of dying with drug X is probably negligible.

Caution in the interpretation of NNT

It should be noted that in practice the interpretation of the NNT should take account of a number of other factors, including how important the consequences of the disease are, the availability of other treatment options, side effects of the treatment and/or its alternatives, costs, patient preferences, etc. It is also useful to note that the NNT is a statistical estimate and, as with any other estimates including the measures described above, the uncertainty in the estimated NNT should be accompanied by a confidence interval.⁵

EXTRAPOLATING PUBLISHED ABSOLUTE RISK MEASURES

Despite the obvious advantages of absolute risk measures, it should be noted that because they are dependent on baseline risk, they are of limited generalisability and it would, for example, be inappropriate to extrapolate published absolute risk measures from one population to another population with a different baseline risk. The calculated ARR and NNT apply only to populations whose baseline risk (in our example, the incidence of hospitalisations due to RSV infection in high risk infants) is similar to the study population. However, if the baseline risk (P_0) of a particular population is known, one can take advantage of the fact that published RR on the topic is likely to be similar across different levels of baseline risk, and calculate ARR for your particular population using the formula: $ARR = P_0 \times (1 - RR)$. The calculated ARR can then be used to estimate the NNT for your population.

For example, if from an audit in your hospital, you estimate the baseline risk of hospitalisations due to RSV infection in high risk infants (P_0) to be, say 15% or 0.15, you can calculate your local ARR as $0.15 \times (1 - 0.45)$ or 0.083 or 8.3%. The NNT for your high risk infants with regard to hospitalisations due to RSV infections for children who received palivizumab compared with those who received placebo will then be $1/0.083$ or 12. This will mean that in your population, about 12 high risk infants need to receive the stated dose of prophylactic palivizumab in order to prevent

one of them from being admitted to hospital with an RSV related illness.

In summary, absolute risk measures such as ARR and NNT are better at discriminating between large and small treatment effects and are more useful than relative risk measures in reports describing outcomes in clinical trials. We should refrain from directly extrapolating published absolute risk measures to other populations with different baseline risks. Knowledge of local baseline risk would, however, allow the calculation of ARR or NNT specific to your local population.

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STAMPS IN PAEDIATRICS

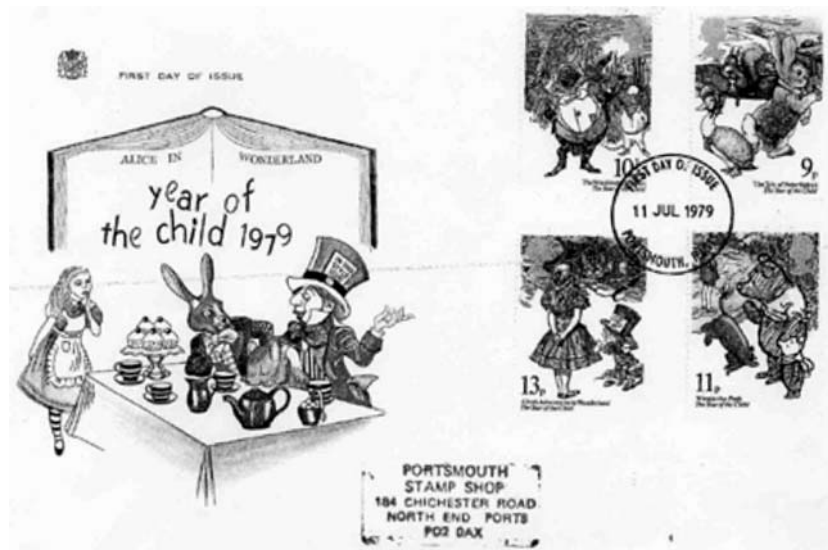
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Year of the Child

In 1959 UNICEF published a Declaration of the Rights of the Child in which it was stated: "mankind owes the Child the best it has to give the child, by reason of his physical and mental immaturity, needs special safeguards and care, including appropriate legal protection, before as well as after birth." The Declaration further specified that all children have the right to affection, love, understanding, adequate nutrition and medical care, education, full opportunity for play and recreation, a name and a nationality, special care if handicapped, be among the first to receive aid in time of disaster, learn to be useful members of society and to develop individual abilities, be brought up in a spirit of peace and universal brotherhood, and enjoy these rights regardless of race, colour, sex, religion, or national or social origin.

In 1976 the UN declared that the world should celebrate children by holding an "International Year of the Child" in 1979. It was supported in many countries, including, despite a little reluctance from the Conservative Government, the UK. Many British organisations were involved, such as the National Children's Bureau (NCB), Barnado's, and the British Paediatric Association (BPA). Like many other countries, Great Britain issued a set of stamps to mark the occasion. The main event of the year was a party in Hyde Park, London for disabled children attended by the Prime Minister Mrs Margaret Thatcher.

Ten years later the UN Convention on the Rights of the Child, based on the 1959 Declaration, was adopted by the full General Assembly and entered into force on 2 September 1990. The Convention was ratified and accepted as a binding obligation by virtually every country in the world. Two additional protocols, on the involvement of



children in armed conflict and on the sale of children, child prostitution, and child pornography, were adopted in 2002.

Since 1979 children have slowly but surely crept up the political agenda in the UK, pushed by organisations such as the BPA (later the Royal College of Paediatrics and Child Health) and the NCB. The Children Act (1989) was a major step forward, and more recently a paediatrician was appointed National Clinical Director for Children (2001), a Minister of State for Children was created (2003), a Government Green Paper "Every Child Matters", was published (2003), and a National Service Framework for children is anticipated soon which will set out standards for child health care. It has taken 25 years to get from the Year of the Child to this stage but, being an optimist, I hope that there is now a real significant change in the recognition of the crucial importance of children's welfare and it will not be another 25 years before there is effective action.

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