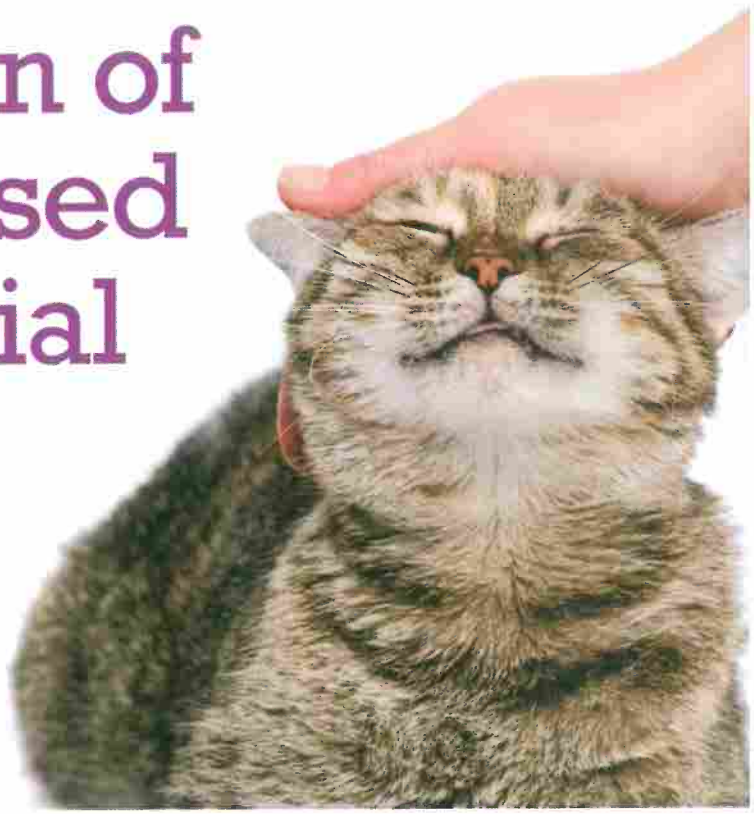
The invention of the randomised controlled trial



Testing new medicines on people randomly assigned to either treatments or controls is the gold standard in modern medicine. Such trials are the closest approximation to the controlled, experimental methods that biologists use in the laboratory. Medical historian Carsten Timmermann explains that their development started in the 1940s, when a new antibiotic was tested for the treatment of tuberculosis

Key words

Antibiotics
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Epidemiology
Medical history

We all want our medicine to be based on evidence. But not all evidence is equal. The pioneers of evidence-based medicine were suspicious of personal experiences of doctors, or even series of systematic observations recorded by clinical researchers. They thought these were unreliable, and susceptible to all sorts of bias. Let's examine why.

Of coughs and cats

Imagine that your grandmother has a bad cough, and you see that her cough improves after she strokes your cat. You may think that this observation provides you with evidence that stroking cats helps cure coughs — but this is not strong evidence. Even if you observe this two or three times, the evidence is not robust. You may be biased, for example, because you have long believed in the power of stroking cats, or you may misinterpret coincidental improvements in your grandmother's condition.

To make sure that your hypothesis is correct, you could get in touch with, say, a hundred coughing grandmothers. First you have to make sure that they suffer from the same kind of cough and, thus, are eligible to take part in your trial. Then you take a dice and roll it to assign each of the grandmothers to one of two groups. 1s, 3s and 5s join the treatment group A; 2s, 4s and 6s join the comparison (control) group B. Then you make all grandmothers in group A stroke a cat and all those in group B stroke a teddy bear. If a clear majority of grandmothers in group A stop coughing more quickly than those in group B, you have generated good evidence that stroking a cat helps cure coughs.

Not so straightforward

Unfortunately, there are some factors that complicate matters. For example, you should specify criteria for the kinds of grandmothers and cats that should be included in the trial (e.g. their age). You should make sure that the grandmothers have all been diagnosed with the same condition and are at the same stage of infection. You will need a good definition of what constitutes significant improvement in a grandmother's condition. You will need to describe in detail how the cat needs to be stroked and for how long. These and many other details need to be specified clearly in your plan for the trial — the so-called 'protocol'. You also have to make sure that the grandmothers comply with the instructions in the protocol. All this is not trivial — and there may be ethical concerns. If you know that stroking a cat helps, can you justify making a coughing grandmother stroke a teddy?

This may sound like a silly example, but the complications it illustrates are not very different from the problems faced by real trial organisers. Let's move back in time to the first modern randomised clinical trial ever organised.

Epidemiology and statistics: the backbone of clinical trials

The study was organised in the late 1940s by clinical researchers working for the British Medical Research Council (MRC) to test a new antibiotic — streptomycin (see Box 1). One of the key members of the team was an epidemiologist. You may wonder what epidemiology has to do with clinical trials — isn't epidemiology the science of epidemics? It is indeed — epidemiologists try to understand how diseases such as cholera spread through populations. By the 1940s, people in industrialised countries were no longer dying predominantly from infectious diseases. Increasingly they were dying from heart disease or cancer, and the causes of

these diseases proved to be much more difficult to identify than those that resulted from infections. Epidemiologists developed a whole new toolkit of sophisticated statistical methods to work out what factors cause heart disease and cancer.

One thing they were studying was the statistical associations between a person's smoking habits and lung cancer. Think about it — not everybody who smokes gets lung cancer. In order to reveal a causal relationship, you have to study a lot of people. If you study a whole population, you can show that significantly more smokers develop lung cancer than those who don't smoke. The statistical methods that epidemiologists developed for such purposes came in handy when some of their colleagues — clinical researchers — wanted to test the effectiveness of the new antibiotic streptomycin. But why, you may ask, do we need sophisticated statistical methods to know if an antibiotic works? Surely people either get well or they don't?

Actually it depends on the antibiotic and the disease. Sometimes a drug does not make all patients better, and it may not even be that obvious if a patient does get better. In such cases, it helps to look at lots of patients — populations. In the 1940s, the amazing effects of the new antibiotic penicillin triggered an excited search for other antibiotics. We needed antibiotics effective in the treatment of conditions where penicillin did not help. As penicillin was a substance produced by a common mould, *Penicillium*, researchers were keenly looking for other antibiotic substances produced by microorganisms.

Streptomycin

One of the laboratories involved in the hunt for new antibiotics was that of Selman Waksman in the Department of Biochemistry and Microbiology at Rutgers University. Waksman was an expert on Actinomycetes — a group of microorganisms that live in soil and decaying vegetation (they are the source of the earthy smell of freshly ploughed fields). In 1943, one of Waksman's graduate students, Albert Schatz, identified two strains of an Actinomycete called *Streptomyces* that stopped the growth of the bacteria that cause tuberculosis (TB) in a Petri dish. This was as exciting as a cure for cancer would be today — TB was the biggest killer of people in the nineteenth and early twentieth centuries, and TB bacteria are unaffected by penicillin.

A substance isolated from cultures of these microbes, which Waksman named streptomycin, also inhibited TB in guinea pigs. But there was no guarantee, of course, that a substance killing TB bacteria in the laboratory would also cure people of TB. While the first tests undertaken in the USA were promising, streptomycin had to be given to patients over long periods, making it difficult to decide whether the benefits outweighed the risk of suffering side effects. This is where the randomised clinical trial came in.

The streptomycin trial

In the summer of 1946 the British Ministry of Health asked the MRC to organise a clinical trial of streptomycin. Production had started in the USA, and some British

Box 1 How does streptomycin work and how is it produced?

A good antibiotic works by killing the cells of a microorganism, while ideally not interfering with processes in our own cells. Bacteria are prokaryotes and have 70S ribosomes, which differ from the 80S ribosomes of eukaryotes such as ourselves. Streptomcyin interferes with protein synthesis in bacteria (see Figure 1.1). It binds to the bacterial ribosome and stops transfer RNA molecules from being released after delivering their peptides to the mRNA template, where the new protein molecule is being assembled. The tRNA is stuck, the next tRNA molecule can't bind, so protein synthesis stalls. As it can't synthesise proteins, the bacterial cell dies.

Once the first trials had shown that streptomycin worked, production had to be scaled up. Like penicillin it's a substance generated by microorganisms. If you only need a few grams for tests, you can isolate this from cultures grown in the lab, using standard flasks and beakers. But if you want to produce it for the world market, you need tons. The first production step was to incubate *Streptomyces* in large fermenters filled with the right growth medium at the optimal temperature, pH, nutrient levels and gas pressures. This was more like beer brewing than the chemical processes that pharmaceutical companies were used to in the 1940s. Fortunately, companies had started to develop the necessary technology for the production of penicillin a few years earlier.

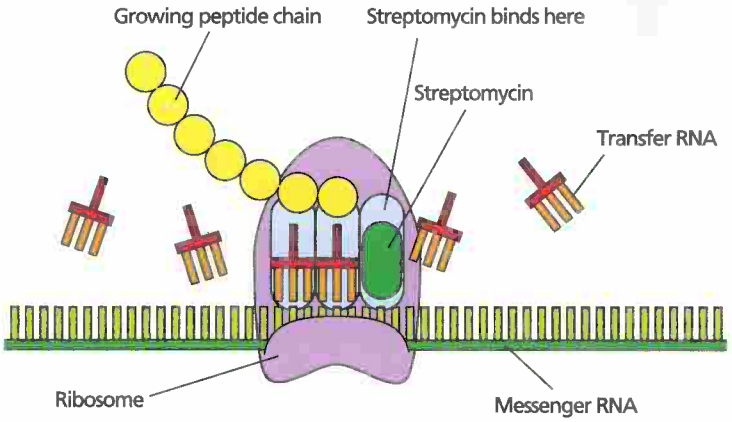
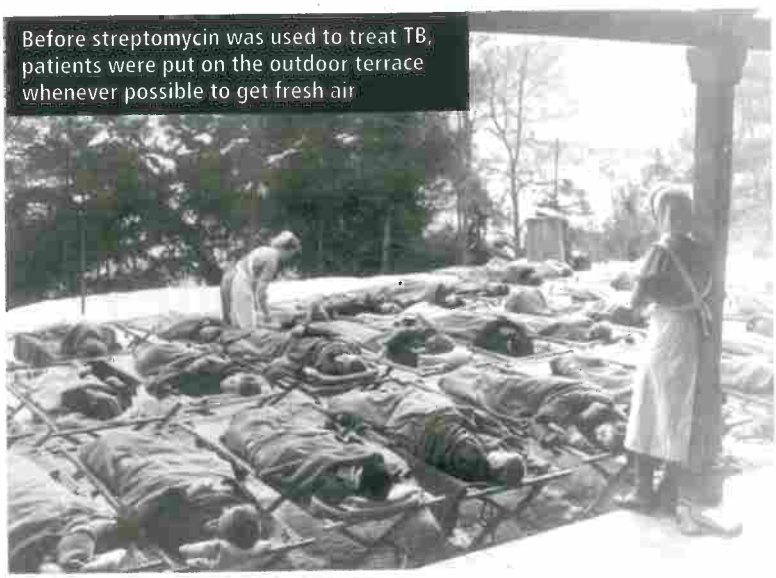
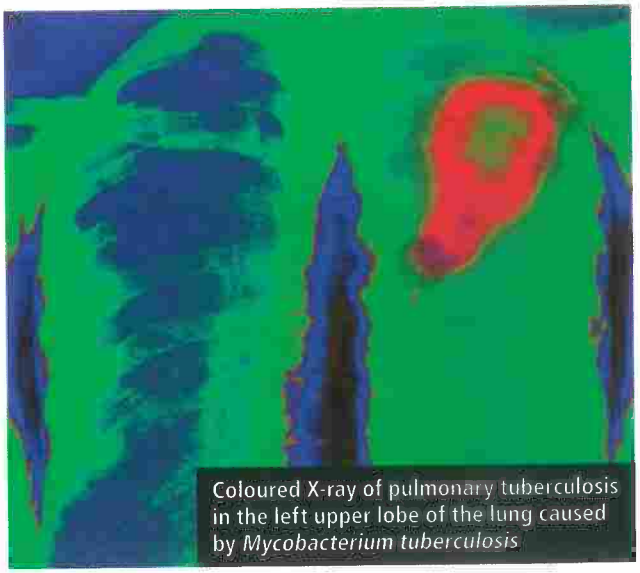


Figure 1.1 How streptomycin works on bacterial ribosomes


Streptomyces fungus in culture ×16



Before streptomycin was used to treat TB, patients were put on the outdoor terrace whenever possible to get fresh air



Coloured X-ray of pulmonary tuberculosis in the left upper lobe of the lung caused by *Mycobacterium tuberculosis*

companies were preparing to produce the drug too, but streptomycin was in very short supply (see Box 1). A team of researchers started to organise the trial in October, advised by the epidemiologist Austin Bradford Hill. He had long been interested in the design of clinical experiments and the application of statistical methods in the clinic. Comparisons between groups of patients, a treatment and a control group, were not new. For example, patients may have been assigned to the different groups by alternating them. So the first patient admitted to the clinic would receive the treatment, the next would be assigned to the control group, and so on. For the streptomycin trial, however, Bradford Hill devised a new system relying on random numbers, by which patients were assigned to different groups. The treatment group received streptomycin plus bed-rest. The control group were prescribed bed-rest alone — which was at that time the established treatment method.

The supply shortage helped overcome an ethical problem. There was not enough streptomycin available to treat all the patients, and randomisation meant that the treating physicians did not have to decide which among the equally deserving patients would receive the new drug.

The ethics of randomised controlled trials

In addition to being a robust method for evaluating the effect of the new drug, randomisation turned out to be the most practical, fairest and most ethical way of rationing streptomycin. This points to an important problem facing organisers of randomised trials. Trials may be methodologically sound, but the circumstances can make them either unethical or impractical (see Box 2).

The results of the streptomycin trial were published in 1948. Comparison of the outcomes between the two randomly allocated groups showed that the drug cured TB if applied correctly. But things could have turned out differently. There could have been unexpected side effects resulting in worse outcomes for the patients treated with streptomycin than those prescribed bed-rest alone. The same, of course, still applies to trials of new medicines today. While a new medicine may propose new hope to patients, there is always the possibility that those treated with the new drug fare worse than those receiving standard treatment. A well-organised randomised controlled trial will reveal if this is case.

Box 2 How do trials conducted today differ from the streptomycin trial?

The streptomycin trial made history. It is celebrated as the first modern randomised clinical trial. But certain aspects of the streptomycin trial were different from many clinical studies conducted today. The streptomycin trial was not placebo-controlled because this would have meant administering to patients in the control group several painful injections of saline solution (a placebo) per day without any benefit to them, which the organisers considered to be unethical. And thus it was also not **double-blind** — patients knew whether they were in the treatment group or in the control group, and so did the doctors treating them. Also, the organisers of the streptomycin trial did not obtain formal informed consent from patients, an omission that would be unthinkable today (see Biological Sciences Review, Vol. 27, No. 1, pp. 26–29).

Further reading

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