IN FOR THE LONG HAUL

Large cohort studies have provided many valuable data. **Geoff Watts** looks at the their future

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The 1946 cohort study of newborn babies inspired similar work all over the globe

Of all the methods used for research, the long term cohort study is the most seductive. You identify a group of people who share a date or place of birth or an experience of some kind, then study them over a period of time. Simple—at least in principle. In practice, because the best known cohort studies have also been very large, the logistical effort required to keep the show on the road is impressive in itself. So impressive that you can almost find yourself viewing any useful insights that emerge more as a bonus than the point of the exercise.

Next month sees the 65th birthday of the granddaddy of all cohort studies, the National Survey of Health and Development.[1] Set up by James Douglas less than a year after the end of the second world war, it began with interviews of more than 13 000 mothers who had given birth in the United Kingdom during one week of March 1946. Concern over the low birth weight of babies born to less well-off mothers prompted a follow-up survey of more than 5000 of the original offspring. The project just kept on going. When the latest assessment began a few years ago its organisers were still in touch with around 3000 of the cohort.

The success of the project has inspired comparable work in several other countries from Finland to New Zealand, and also further cohort studies in the UK. These include the 1958 National Child Development Study, the 1970 British Cohort Study, and the Millennium Cohort started in 2000.[2] But although birth studies of this kind are the most publicised use of the cohort approach, it can be applied to any large group being investigated for all manner of reasons. The European Prospective Investigation of Cancer and Nutrition (EPIC), for example, is studying 500 000 people in 10 European countries to investigate whether cancer is related to diet.[3]

And further studies keep emerging. The French government has recently funded a study led by epidemiologist Tobias Kurth, a director of research at Inserm (the country's health and medical research institute) and *BMJ* consulting clinical epidemiology editor. It will follow 30 000 students from the universities of Bordeaux and Versailles for at least 10 years. "We'll look at disorders that are most frequent in this age group, especially mental health disorders such as depression," says Dr Kurth. "We'll also look at migraine, which often starts between 20 and 30. We'll look for risk factors which might explain the disease onset. And since we're planning a long follow-up, we'll also look for risk factors for diseases that develop later in life."

Strength of time

The potential of these studies as research tools is clear. Although randomised controlled trials are usually regarded as the best method for tackling research questions, there are circumstances in which they are impossible or simply unethical. Testing the effects of asbestos or tobacco smoke on health are obvious examples. Moreover, following people for many years, or even a lifetime, makes it possible to explore their development, health, or ageing in relation to changes in their personal circumstances or the wider economic and social environment. But that said, do the findings really justify the considerable time and resources that cohort studies absorb?

That many of the biggest are so familiar is an indication of their impact. Think, for example, of Richard Doll's study of smoking in 35 000 British doctors.[4] From 1951 it tracked their mortality for 50 years and showed the increased risk of vascular and respiratory diseases and cancer associated with cigarettes. Think of the Whitehall studies of British civil servants[5] and their telling illumination of the differing prevalence of ischaemic heart disease at different levels in the hierarchy. And think of the "natural" experiments at Hiroshima and Nagasaki that generated two cohorts exposed to intense bursts of radiation.[6]

More specifically, the National Survey of Health and Development claims to have informed all manner of official reports including, in the health field, the 1998 Acheson report on inequalities in health,[7] and the more recent review of the topic by Michael Marmot.[8] Diana Kuh, director of the national survey, believes that it has been particularly influential in reinforcing the view that what happens in your early years affects your adult life. "In the middle period of the study there was a raft of papers showing associations that seem to be important. This really influenced popular thinking that investing in children is important for later life."

The survey has now reached a point at which its cohort will soon start to become elderly. "We're a study that can tell the government about the likely impact of ageing on health and social services," says Professor Kuh. The data will reveal the extent to which a poor start in life is still affecting the health of 60 year olds. In due course it will also find out whether the influence persists into people's 70s—or if by then it's faded or been swamped by other factors.

The Millennium Cohort Study, which has been going only a decade, isn't yet in the same league of proved achievement. But it

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Advantages and drawbacks of cohort studies

An Academy of Medical Sciences working party listed some of the pros and cons of cohort studies.[9] They included:

ADVANTAGES

The sequence and timing of associations are readily determined

There is no need to rely on long term retrospective recall

They provide a ready estimation of the size of an effect

There is a good opportunity to examine a wide range of both expected and unexpected outcomes

DRAWBACKS

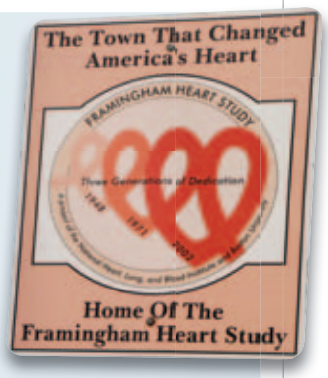
Very large samples are required if the disease outcomes to be examined are uncommon

A long time frame is needed to study most associations with disease

Two notable US cohort studies

FRAMINGHAM HEART STUDY

The study began in 1948 when researchers recruited more than 5000 people from the small Massachusetts town of Framingham (www.framinghamheartstudy.org/index.html). Every two years they have a physical examination and laboratory tests. A second generation was recruited in 1971 from among the original participants' adult children and their spouses. And more recently some of the grandchildren of the original cohort were enrolled. The issues that the Framingham data have clarified or brought to light include the influence of smoking, cholesterol, blood pressure, physical activity, and obesity on heart disease and stroke.



NURSES' HEALTH STUDY

Established in 1976 to investigate the potential long term consequences of oral contraceptives, the study's 122 000 nurses answered questions about smoking, hormone use, and diet (www.channing.harvard.edu/nhs/). A second cohort was added in 1989 and a third in 2008. These studies have explored the influence of smoking, oral contraceptives, alcohol, obesity, and physical activity on heart disease, breast and colon cancer, hip fracture, and cognitive function.

has already carried out four surveys of its 19 000 children. Published analyses include the factors that predispose to the emergence of obesity (children who don't have breakfast are more likely to be overweight) and the influence of breast feeding on health, says its director, Lucinda Platt. "It can be difficult to point to any particular finding and say that this changed that policy. But the policy community is very much aware of what comes out of these surveys."

Qualified results

Although cohort studies provide data that may, in some cases, be difficult to obtain by experimental methods, they do have their limitations. In its 2007 report on observational methods in medical research,[9] the Academy of Medical Sciences offered the example of folic acid intake during early pregnancy to prevent neural tube defects. In 1989 a cohort study of 23 000 births pointed to a large and specific benefit of the maternal use of folic acid supplements during the first six weeks of pregnancy. The prevalence of neural tube defects was four times higher in children born to women who had not taken folic acid or who had taken it later in pregnancy than among those born to women who had taken it in the first six weeks. But while the study showed a clear association, it couldn't prove causation. As the academy report points out, it could have been that "high social class women at low risk were more likely to take vitamins." It took a randomised controlled trial to establish the causal connection.[10]

Nor do all new cohort studies receive an unqualified welcome. The 500 000 strong UK Biobank (www.ukbiobank.ac.uk) has been set up to investigate people's illnesses in relation to their genes and their environment. But critics have accused its organisers of lacking clear objectives and of collecting social information that won't be as robust as the molecular data.

In spite of occasional criticism, cohort studies clearly have a future. While some can provide virtually definitive evidence (no point, for example, in rerunning the doctors and smoking study), the conclusions of others will always be provisional. The birth cohorts, for example. "We know from previous cohorts how early life experiences have influenced adults who are now in their 50s," says Professor Platt. "But the world's changing, gender attitudes are changing, the education system and the economic climate have changed." You don't have to be a sociologist to know that the life of a child born in the years after the second world war is vastly different from that of a child born this century. So enthusiasts for birth cohort studies can make a powerful case that their projects have to be reinvented and repeated again and again. Judgments of what matters evolve, as do the issues themselves. You can't look to a study that began even as recently as 20 years ago to find out how hours spent peering at a computer screen instead of kicking a football might be affecting physical and mental health.

Adaptation

Britain has accumulated a wealth of longitudinal data. A project called HALCyon (Healthy Ageing across the Life Course, www.halcyon.ac.uk) is now linking the National Survey of Health and Development with eight other UK cohort studies. The aim is to understand more about how ageing affects physical and cognitive abilities and psychological and social wellbeing, as well as the biology of ageing itself. Four of these studies use information collected during the 1920s and 1930s: a remarkable re-exploitation of data that might otherwise be seen as having only historical interest.

One other thing that is clear about large cohort studies is that you don't embark on them lightly. Reflecting on his forthcoming study of university students, Dr Kurth commented, "Getting people of this age group and following them up is quite challenging." That's putting it mildly. And there's the matter of funding. If your study is really ambitious you can find yourself moving into the realms of "big science." Biobank, for example, is costing around £60m (€70m; $97m). And if you aim to keep going for a seriously long time, you must learn the arts of adaptability. Having started in the 1940s the National Survey of Health and Development has witnessed every advance in data storage and handling from index cards through to desktop computing. But it's kept going.

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Challenges of implementing human papillomavirus (HPV) vaccination policy (*BMJ* 2007;335:375)

HPV: beyond the rich world

Most deaths from cervical cancer occur in countries without the resources to screen, treat, or vaccinate against the disease. **Sophie Arie** explores what's being done to make HPV vaccination available to low income countries

In roughly five years since they arrived on the market, vaccines against human papillomavirus (HPV), which causes cervical cancer, have been rapidly and widely adopted in countries that can afford to do so.

The United States and much of Europe have introduced vaccines for school age girls in addition to existing well established screening programmes for women. The vaccines—Cervarix, made by GlaxoSmithKline (GSK), and Gardasil, made by Merck—protect against the most common types of virus, which cause around 70% of all cervical cancers, but they are among the most expensive of all vaccines. Both companies say their prices reflect a major investment in research and development and relatively complex manufacturing processes. Pricing varies from country to country but the current price in the US for a three dose course of Cervarix is a little under $300 (£187; €222) for government health service providers and close to $360 for private healthcare providers.[1]

"Although price is the largest obstacle, infrastructure, medical expertise, public acceptance, and political will are also problems"

In the developing world, however, the situation is very different. Nearly 530 000 women each year develop cervical cancer and 275 000 die from it.[2] More than 85% of those deaths occur in low and middle income countries, where cervical cancer is the most common type of cancer in women, but screening is usually available only to women who can afford it privately, and where there is little or no capacity to treat the disease, let alone the resources to invest in a vaccine.

More than 60% of women who contract the disease in the developing world die of it because of late detection. According to the World Health Organization, if current trends continue, the incidence of cervical cancer worldwide will rise to an estimated one million cases by 2050 and the numbers of deaths from cervical cancer will rise by nearly 25% in the next 10 years. By 2020, 90% of those deaths will be in the developing world.[3]

Efforts are afoot to do something about this. WHO, Unicef, and organisations such as the Bill & Melinda Gates Foundation and GAVI (the Global Alliance for Vaccines and Immunisation) are all working to make vaccine available in the countries that need it most. In 2008, GAVI identified HPV vaccine as one of those that would have the biggest impact on disease burden in developing countries. It is thought that widespread vaccination could at least halve the number of cases of cervical cancer over the next 50 years. But with current available prices, GAVI has not been able to raise the funds needed to roll out vaccination across member countries.

GSK and Merck say they are keen to help make vaccine available to developing countries. Merck pledged in 2007 to donate at least three million doses of its vaccine, Gardasil, through its charitable access programme, and it is currently working with US biological technology company Qiagen to create new technology for a comprehensive programme of HPV vaccination, HPV DNA testing, cervical cancer screening, and treatment. Both companies have introduced price tiering systems so that they can offer vaccine to lower income countries at a lower price than elsewhere. Merck claims that as a result of this kind of negotiation, last year the Kingdom of Bhutan became the first developing country to implement a national cervical cancer programme.

Governments of countries such as the Philippines, Vietnam, Indonesia, Colombia, Ecuador, South Africa, and Nigeria have secured lower prices with GSK by committing to purchase enough for the entire birth cohort over a large number of years, says Thomas Breuer, head of global vaccine development, based at the company's vaccine headquarters in Belgium.

"It is very important—and the more governments talk to us and the more contracts we have which are long term in duration and with a fixed volume the better position we are in to go down with the price," says Dr Breuer.

By securing high volume long term contracts, GSK has been able recently to offer prices to low income countries that are between 40% and 70% of those paid by the wealthiest countries. Competition between the two manufacturers of HPV vaccines also means the price is gradually falling globally, but still not enough to be affordable for many countries.

Calculations suggest that if HPV vaccine could be made available at $10 per course to countries with no existing screening programme, introduction would be cost effective in terms of the sums saved by reducing the burden of the disease on

ANUPAM NATH/AP/PA

A young women is given the HPV vaccination in Gauhati, India, April 2010

health services. A vaccination programme would even be cost effective for some countries at a higher price, but not at the current prices.[3]

Although price is the largest obstacle, infrastructure, medical expertise, public acceptance, and political will are also problems in many countries.

PATH, a Seattle based non-governmental organisation with funding from the Gates Foundation, is working with local governments to explore the feasibility of introducing HPV vaccine in four countries: Uganda, Vietnam, India, and Peru.

In Uganda, a two year feasibility study concluded that the existing health system could be used to deliver through schools or special vaccination days.

But in India, which accounts for 20% of annual deaths from the disease, a study in which 23 500 girls were vaccinated in Andhra Pradesh and Gujarat had to be suspended in 2010 because of objections raised by influential media commentators, non-governmental organisations, and scientists over possible unknown side effects. Four girls died during the study, and although it has since been established that their deaths were not related to vaccination, the Indian government is still running an inquiry to respond to the concerns raised.

Growing awareness in developing countries of cancer in general—perhaps because of populations becoming better informed through the internet—means that cervical cancer is rising up the list of public health priorities for many governments.

But public distrust of a vaccine made by a multinational drug firm and promoted by foreign aid agencies means that the governments of countries like India and Brazil are keen to develop their own versions of HPV vaccine.

Brazil has purchased Cervarix and begun a vaccination programme but at the same time—as it has done in the past with measles, rotavirus, and HIV vaccines—it intends to develop and produce its own generic vaccine at the facilities run by the state's vaccine institute, Fiocruz. Companies in India are also aiming to develop their own HPV vaccines, although GSK believes it will take many years before any can produce something as complex and of the same quality as Cervarix.

Several US scientific institutions are also working to develop cheaper alternatives. Bob Garcea, professor in molecular, cellular, and developmental biology at the University of Colorado, hopes to begin clinical trials of a vaccine he has developed, which he claims has proved as effective as Gardasil and Cervarix in preclinical trials. He hopes that by using subunits called capsomeres to make the vaccine, rather than virus-like particles made from HPV proteins, the cost of manufacturing can be reduced dramatically. His goal is to create a vaccine that would cost $1 a dose.

However, funding problems are slowing down the clinical trial process and he expects it to take at best another five years to complete clinical trials. Richard B S Roden, an associate professor of pathology, gynaecology and obstetrics, and oncology at Johns Hopkins University, is also hopeful that a synthetic vaccine his team has created to be delivered as a nasal spray could protect against all HPV types and be produced at an affordable price.

But progress in this sort of research is slow, and biochemical companies and drug firms are not rushing to fund trials, possibly because of concerns over potential intellectual property disputes with GSK and Merck.

Some experts believe, however, that even if a high quality affordable generic vaccine becomes available, many of the poorest countries will not buy it because the effect of vaccination on morbidity and mortality will not be seen for another 20 or 30 years.

"On paper, to us (in the West) vaccination seems the best way to prevent the disease," says Dr Mario Sideri, director of preventive gynaecology at the European Institute of Oncology in Milan. "It's an investment for the future. But these countries need to see mortality rates fall much sooner."

"Cancer is an emerging issue in many countries," says Dr Sideri. In a country like Madagascar, the new government has made public health a high priority and wants to tackle cervical cancer. But given a choice of where to put their scarce resources, Madagascar and similar countries are more likely to invest in screening, proper treatment and palliative care than in prevention of the disease.

Dr Sideri is involved in research into a low cost form of cervical cancer screening that Madagascar could adopt.

"The government there is telling us 'we need to propose something that we can afford and that will benefit the whole country,'" he says.

Vaccination in such countries, where most cervical cancer cases are detected too late to be cured, can be considered only in tandem with screening programmes.

Meanwhile, if Merck succeeds in developing a new generation vaccine that protects against almost all types of HPV (it hopes to do this by 2012), Western countries will gradually be able to depend less and less on screening.

"In Europe we will have fewer and fewer cases of cervical cancer," says Dr Sideri. "The challenge will be to transfer our knowledge to the parts of the world that are only just approaching the problem."

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