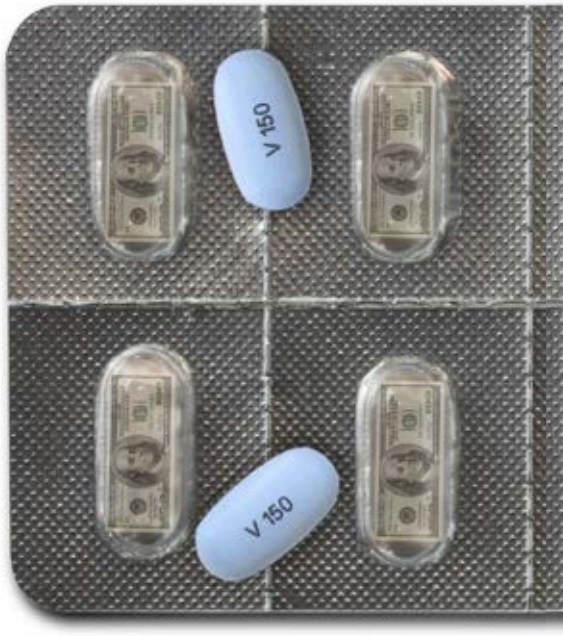


bmj.com See more articles about orphan drugs on our cluster page at bmj.com/article-clusters

Paying twice: the "charitable" drug with a high price tag

Deborah Cohen and **James Raftery** ask why one of the first medicines to be developed by a partnership between a charity and a drug company ended up being one of the world's most expensive drugs. Why didn't such philanthropy lead to affordable access?

In early 2012, the first drug targeting the underlying cause of cystic fibrosis was approved in Europe and the United States. Ivacaftor's (Kalydeco) arrival was greeted with a flurry of excitement.

Billed as a "game changer" by industry pundits and "a profoundly exciting development" by National Institutes of Health director, Francis Collins, ivacaftor soon became one of the world's most expensive medicines—its mode of action considered as exciting as its unique funding model. Ivacaftor was approved for a rare group of patients who carry the genetic mutation, G551D, in the cystic fibrosis transmembrane regulator (CFTR) gene—about 5% of people with the disease.[1] Mutations in the CFTR protein, which regulates ion—and therefore water—transport in the body, lead to the formation of thick mucus in the lungs, digestive tract, and other parts of the body. Ivacaftor facilitates increased chloride transport in people with the G551D mutation, and in trials it was found to improve forced expiratory volume. Trial participants also had fewer exacerbations and put on weight.

The US Food and Drug Administration was quick to add its support for the drug. "Kalydeco is an excellent example of the promise of personalized medicine—targeted drugs that treat patients with a specific genetic makeup," FDA commissioner, Margaret Hamburg, said when it was licensed. "The unique and mutually beneficial partnership that led to the approval of Kalydeco serves as a great model for what companies and patient groups can achieve if they collaborate on drug development."[2]

New model of funding

Ivacaftor is the first drug developed through "venture philanthropy"—a partnership between a charity and a drug company. It's an emerging trend in drug development, particularly for rare conditions, whereby a non-profit organisation helps to finance the development of a treatment in return for a share in profits.

A 2007 report in Centerwatch, an industry publication, found that investment through venture philanthropy had risen 10-fold since 2001.[3] One of the reasons for this rise, according to representatives of the US Muscular Dystrophy Association and the Juvenile Diabetes Research Foundation, is that although academics may discover important compounds, industry is more adept at clinical translation.[3]

These organisations are two of several engaging in their own drug research and development. Although this model is gaining attention as a means to bring treatments for rarer conditions onto the market, the concept is nothing new. Over 75 years ago, the US National Foundation for Infantile Paralysis engaged in venture philanthropy. It funded much of the research that led to the development of the polio vaccine and was supported by public donations.[4]

Although the gene that causes cystic fibrosis was identified in 1989 by publicly funded researchers, drug companies were not interested in developing a drug that targeted the underlying cause—investing in research and development was considered to be a high financial risk. That all changed when a US charity, the Cystic Fibrosis Foundation, entered the fray. In 2000, the charity established an affiliated research arm to govern drug discovery aided by a grant from the Gates Foundation. It teamed up with Vertex, a small company with a successful record with high risk drugs.

Ivacaftor has been lucrative for the charity. Its royalty income jumped from under $1m in 2011 to $157m in 2012

Barry Werth, a US based journalist, was granted access to Vertex when it was a small start-up in Cambridge, Massachusetts, in the early 1990s. He went back in 2011 when ivacaftor had started to show promising clinical trial results, reported in his book, *The Antidote*.

Werth told the *BMJ* that the Cystic Fibrosis Foundation had approached lots of companies to develop a drug that targeted the underlying cause, but Vertex was the only one willing to give it a go. Over the years, the foundation has given over $75m (£46m; €55m) to Vertex for research and development.

In 2006, the partnership bore fruit—VX-770 (later named ivacaftor) entered clinical trials using the foundation's network of affiliated medical centres. An awareness campaign by the foundation buttressed recruitment.[3] The drug was approved by the US in January 2012 after only three months of review and gained an EU licence seven months later.

Price concerns

But given the level of public financial investment, does this mean that health services—and the donating public—are getting a better deal and more affordable access to such drugs?

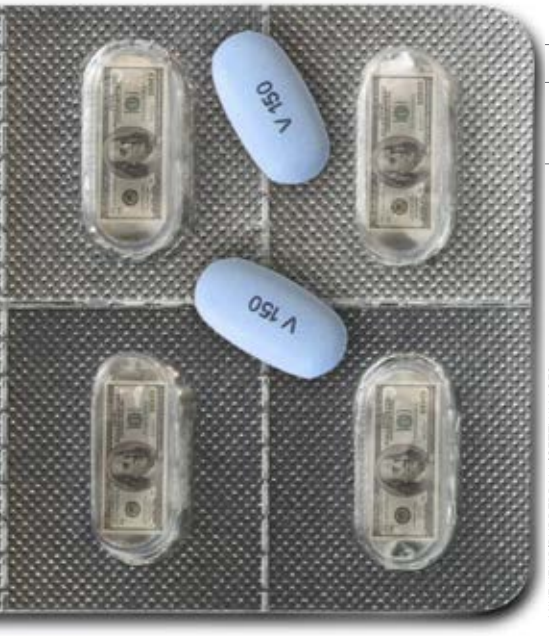
The Cystic Fibrosis Foundation is one of the most successful fundraising charities in the US, partly because of the efforts of businessman Joe O'Donnell, whose son died from cystic fibrosis. In the 30 years since his son died, O'Donnell has raised around $100m by holding film premieres, "hot dog safaris," golf tournaments, and an annual bowling night for financiers.[5]

According to its financial reports, ivacaftor has been lucrative for the charity. Its royalty income jumped from under $1m in 2011 to $157m in 2012—or just over half its income—as a result of their stake in the profits of the drug.[6] On top of the royalties agreed, the foundation gets additional payments for extraordinary sales results.

The foundation say that this money will be poured back into research. Indeed, Vertex too has pledged publicly that it will cure cystic fibrosis by 2020.[7]

"Vertex is now a $20bn company," Werth says. "There is no competition and ivacaftor is on patent until 2025. It doesn't have to worry about other companies. Wall Street loves it."

But on 9 July 2012, 24 US doctors and



MIKE KEMP/RUBBERBALL/GETTY IMAGES

researchers involved in the development of the drug wrote to Vertex to express their dismay at the cost of the drug.

"We have invested our lives and careers toward the success of these inspiring therapeutic agents," the researchers said, adding: "We also write with feelings of dismay and disappointment that the triumph and honor that should be yours is diminished by the unconscionable price assigned to Kalydeco.

"Yet—notwithstanding all your patient support programs—it is at best unseemly for Vertex to charge our patients' insurance plans (including strapped state medical assistance plans), $294 000 annually for two pills a day (a 10-fold increase in a typical patient's total drug costs). This action could appear to be leveraging pain and suffering into huge financial gain for speculators, some of whom were your top executives who reportedly made millions of dollars in a single day."[8]

A spokeswoman from Vertex said that the company's chief executive, Jeff Leiden had subsequently had a series of conversations with the doctors "to help address their concerns and answer questions. He also met with them in person at a medical meeting and there is an open invitation to regroup as needed."

However, since writing the letter and attempts by the doctors to discuss pricing with Vertex, the annual price of the drug has increased by $13 000 to $307 000 a year. This, said a Vertex spokeswoman, took "account our continued investment in the research and development of other potential medicines for CF."

Ed Owen, chief executive of the Cystic Fibrosis Trust in the UK, said that the organisation shared some of the doctors' concerns.

"We recognise that companies like Vertex should rightly expect a return on the considerable investment that is made in developing drugs like ivacaftor. We do, however, share concerns about the long term impact of high cost drugs on the NHS," he said.

Ivacaftor will probably need to be taken for decades by individual patients and the total cost may run into many millions of dollars. In an editorial in JAMA, doctors point out the ethical dimension. "The patients who assumed the risks of participating in the clinical trials necessary to bring this drug to market and who devoted countless hours to raising money for the CF Foundation to underwrite early work are now being asked to pay, most often through their insurers, an exorbitant price for the product that resulted from their efforts," Brian O'Sullivan, a paediatric pulmonologist at the University of Massachusetts Medical School, and colleagues wrote. [1]

Werth told the *BMJ* that Vertex is interested in working with the cystic fibrosis community, but won't discuss pricing.

"They just won't talk about it. The issue here is that access has been separated from pricing. They're setting a high price but making sure that no one goes without by offering the drug free to any patients who can't afford it. So then they charge as much as the market will bear," he said.

But the US is not the only country where the cost has been a concern.

UK situation

In England the North of England Specialised Commissioning Group was asked to examine whether ivacaftor should be funded across the country. In the run up to the group's meeting in 2012 Vertex offered ivacaftor free of charge for a limited period to certain patients. This left hospitals with the ethical dilemma of giving a drug only to have to withdraw it once the company stopped providing it free.

Jessica Nickless, vice-chair of the Ivacaftor Patients Interest Group, is unequivocal about where the blame lies. Commenting on the case of Caroline Cassin, who was refused free treatment by Birmingham's Heartlands Hospital, she told the Daily Telegraph: "If I stood by and witnessed someone being murdered I would be complicit to that murder, yet doctors can watch someone die. They are condemning Caroline to a slow, lingering death.[9]

Access to the drug was later extended to cover patients without a time limit and Caroline received treatment. A spokeswoman for Vertex told the *BMJ* that it did this because it wanted to "provide medicine to patients who are in critical need of treatment and meet certain criteria while these discussions are ongoing."

But, judging by comments on social networking and petitions sites, the reluctance of the health services to pay for ivacaftor has been blamed on governments—not on the pricing decisions made by Vertex and the Cystic Fibrosis Foundation.[10 11]

When ivacaftor was assessed by the North of England Specialised Commissioning Group in 2012 it put the cost per quality adjusted life year (QALY) between £335 000 (optimistic scenario) and £1 274 000 (conservative scenario)—way above the National Institute for Health and Care Excellence thresholds.

Although the discounted price is commercial in confidence, a report shows the commissioners negotiated a discount that put the cost per QALY between £285 000 and £1 077 000—about a 15% reduction.

Given that 320 patients in England have the specific mutation and are considered eligible, the annual cost to the NHS is around £55m per year—a sizable sum of money.

In Scotland, however, ivacaftor was initially offered to people on a named patient basis only and clinicians had to put forward an application for the drug.

Four days after the Scottish Medicines Consortium recommended against funding the drug, Scottish health secretary Alex Neil said that the health services would pay for it. He had met with the Ivacaftor Patient Interest Group. The Cystic Fibrosis Trust also campaigned on the issue.[12-14]

Elsewhere negotiations are tougher. At the start of the year, Vertex told investors that one of their aims was to get public reimbursement in Australia and Canada—where the drug is licensed but the cost has yet to be agreed.[15]

Australia's Pharmaceutical Benefits Advisory Committee initially deferred a decision to fund the drug because of the cost. But just before Christmas, they agreed that it should be funded—leaving the government to negotiate the price.

In the run up to the decision, Cystic Fibrosis Australia coordinated a lobbying campaign concentrating on newly elected members of parliament, shortly after the federal government elections.

In the short term this might be affordable for health systems, but what happens when targeted drugs are developed for more conditions if they are also very expensive and for small populations?

"This move towards personalised medicine raises other serious questions. [Ivacaftor] could be used as a test case to see what challenges are there," said Werth.

Deborah Cohen investigations editor, *BMJ*, London, WC1H 9JR, UK **dcohen@bmj.com**
James Raftery professor of health technology assessment, University of Southampton, Southampton, UK

Competing interests: None declared.
Provenance and peer review: Commissioned; not externally peer reviewed.
References are in the longer version on bmj.com.
Cite this as: *BMJ* 2014;348:g1445

bmj.com Previous data briefing articles

- Are accident and emergency attendances increasing? (*BMJ* 2013;346:f3677)
- Are "friends and family tests" useful: agree, disagree, neither, don't know? (*BMJ* 2013;346:f2960)
- The hospital bed: on its way out? (*BMJ* 2013;346:f1563)

DO WE HAVE TOO MANY HOSPITALS?

The NHS is under repeated pressure to close beds and hospitals. **John Appleby** investigates the true extent of provision and how it compares with that in other countries

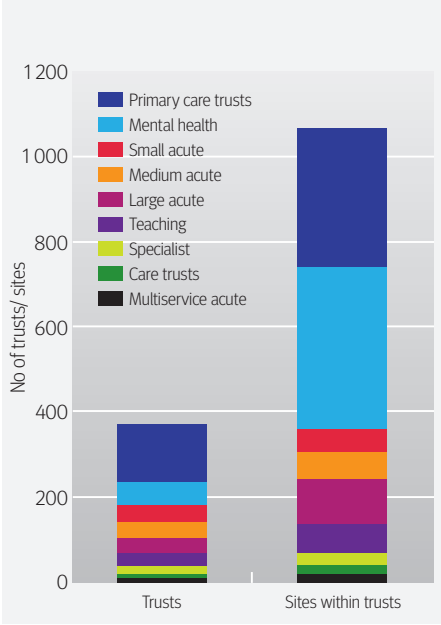


Fig 1 | Number of hospital trusts and sites, England 2010-11 (NHS trusts may comprise more than one hospital site)[6]

London's health services have been subject to major reviews—around one every decade since 1890.[1] Nearly all have suggested that London needed fewer hospital beds and indeed fewer hospitals. A 1980 report reviewing London's health services suggested the capital should lose the equivalent of a 500 bed acute hospital each year for 10 years to get into line with population needs.[2] The Tomlinson inquiry report in 1992 and a King's Fund review in the same year both, among other things, recommended reductions in hospital beds and by implication reductions in the number of hospitals in London.[3 4] *Health Care for London* is the most recent review of the capital's health system, and like its many predecessors recommended fewer hospital beds and fewer hospitals through reorganisation of care into polyclinics and people's own homes.[5] Similar assessments have been made in other conurbations, and the trend seems to be to indicate a move to fewer hospitals.

But how many hospitals are there? How big are they? Indeed, what actually defines a "hospital" and do we really know how many are needed?

For data on NHS hospitals in England the key and only source is ERIC: the estates return information collection[6]—not to be confused or partnered with ERNIE, the Electronic Random Number Indicator Equipment designed to randomly pick premium bond winners (an early British state run lottery/savings system).[7]

ERIC collates information on the NHS estate across England—from the cost of feeding patients each day (£7.47 on average in 2010) and the proportion of "untouched meals" (6.1% on average) to the land occupied by NHS hospitals (around 25 square miles). It also lists and categorises NHS trusts (the management unit) and sites (hospitals). In 2010 ERIC recorded 372 NHS trusts with at least one bed. Nearly 40% of these were primary care trusts—mainly small community hospitals. Around a third were acute trusts of various sizes, 15% were mental health trusts, and 13% were teaching trusts or trusts specialising in particular diseases or patient groups (fig 1).

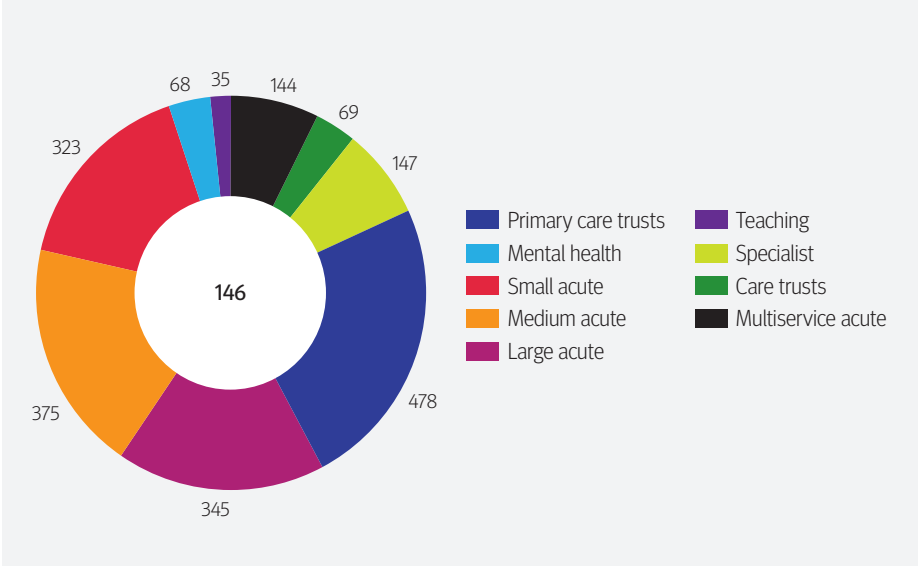


Fig 2 | Average number of beds by type of NHS hospital for 372 trusts with more than one bed, England 2010-11[6]

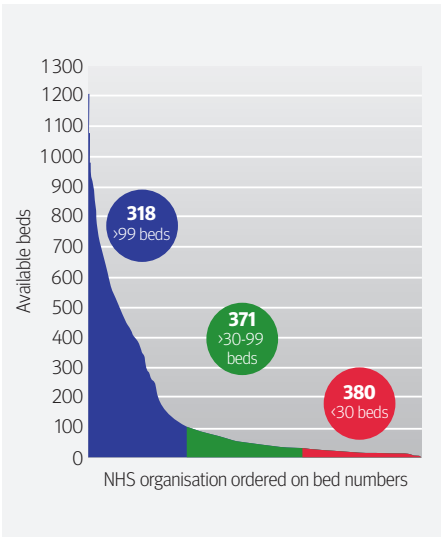


Fig 3 | Number of beds per NHS hospital site, England 2010-11 (1069 sites, includes all types of NHS hospital, from acute to long stay, community and mental health)[6]

What the trust (the "managerial unit") perspective can obscure is the huge number of actual hospitals in existence. Most trusts consist of several hospital "sites" (as the statistics describe them) that over time have become managed as a single business (trust). In 2010, across England, there were over 1000 NHS hospital sites with more than one bed. More than half were small community or mental health facilities with an average of 35 or 68 beds respectively. Just over seven in 10 hospital sites in 2010 had fewer than 100 beds (figs 2 and 3). The largest hospitals are those classified as teaching—an average of 478 beds in 2010.

Internationally there are large variations in the numbers and sizes of hospitals (fig 4). Data from the Organisation for Economic Cooperation and Development (which unfortunately excludes the UK as we have never submitted data on hospital numbers) show the number of hospitals per million population range from around 12 in Israel to 68 in Japan. Similar variations exist for public and non-public hospitals. Even taking a reasonably liberal definition of what counts as a hospital (all hospital sites for all types of hospital with at least one bed), England seems to be less than averagely endowed with hospitals compared with other countries. And its public hospitals tend to be smaller on average than other countries' too (fig 5).

So maybe England has too few hospitals. But beware, the first rule of international comparisons is never to presume that other countries have got it right.

John Appleby chief economist, King's Fund, London, UK
j.appleby@kingsfund.org.uk

Competing interests: None declared.

Provenance and peer review: Commissioned; externally peer reviewed.

1 Appleby J, Ham C, Imison C, Harrison T, Boyle S, et al. Improving health and health care in London: who will take the lead? 2010. www.kingsfund.org.uk/sites/files/kf/Improving-Health-Healthcare-London-Kings-Fund-paper_0.pdf.
2 Briefing: London health planning consortium. *BMJ* 1980;i:734. www.bmj.com/highwire/filestream/250015/field_highwire_article_pdf/0/734.
3 Tomlinson B. Report of the inquiry into London's health service, medical education and research. HMSO, 1992.
4 King's Fund. London health care 2010: changing the future of services in the capital. King's Fund, 1992
5 NHS London. Healthcare for London: a framework for action. 2007. www.nhshistory.net/darzilondon.pdf.
6 Health and Social Care Information Centre. Hospital estates and facilities statistics. 2014. http://hefs.hscic.gov.uk.
7 National Savings and Investment. The history of ERNIE and premium bonds. 2014. www.nsandi.com/savings-premium-bonds-history-ernie-and-premium-bonds.
8 OECD. OECD health statistics 2013. 2014. www.oecd.org/els/health-systems/oecdhealthdata.htm.
9 Private Healthcare Information Network. Personal communication. 20 January 2014.

Cite this as: *BMJ* 2014;348:g1374

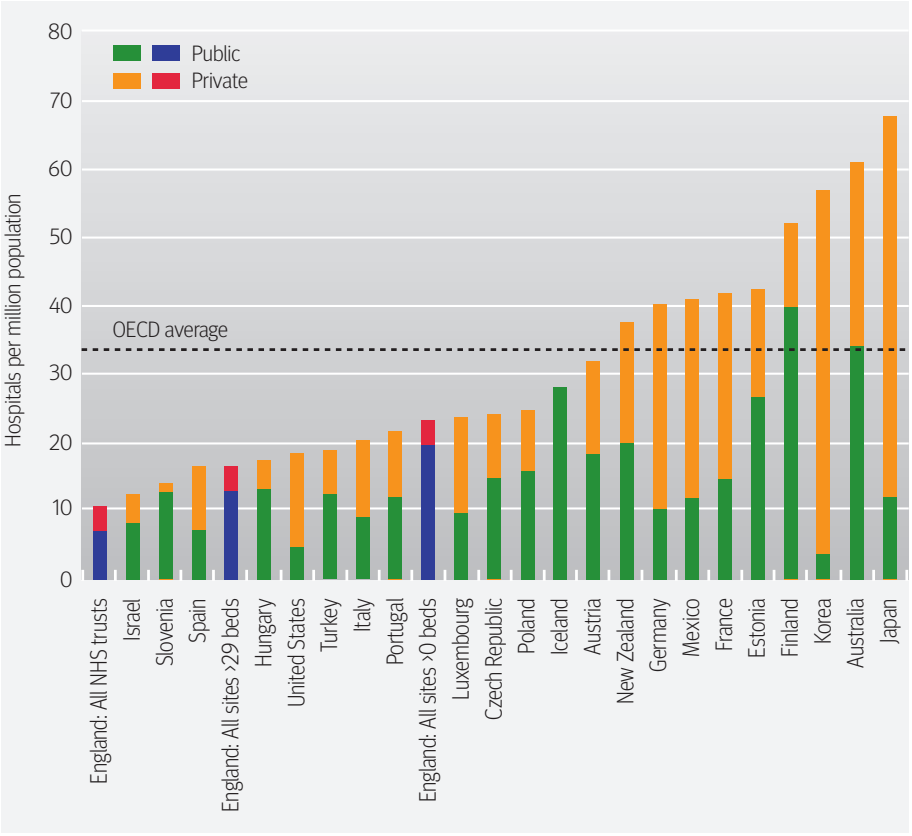


Fig 4 | Hospitals per million population in OECD countries, 2010. (For England, hospital/bed data includes all types of NHS hospital and trusts may comprise several sites. For other countries hospital/bed data for hospitals includes "general, mental health and specialised" hospitals as defined by OECD)[6 8 9]

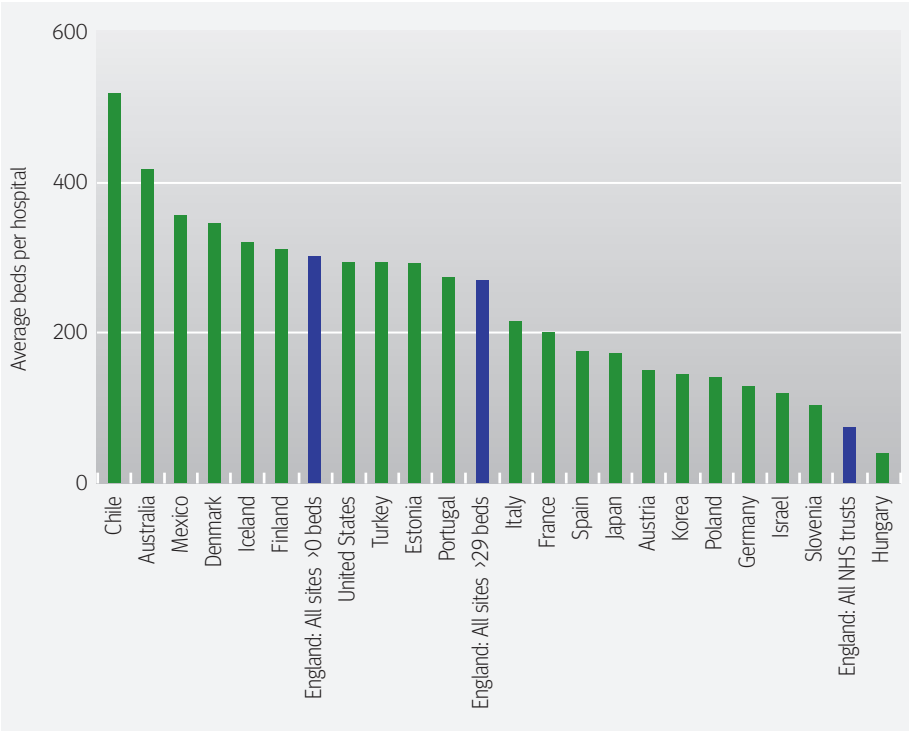


Fig 5 | Average number of beds per public hospital, 2010. (For England, hospital/bed data includes all types of NHS hospital and trusts may comprise several sites. For other countries hospital/bed data for hospitals includes "general, mental health and specialised" hospitals as defined by OECD)[6 8]