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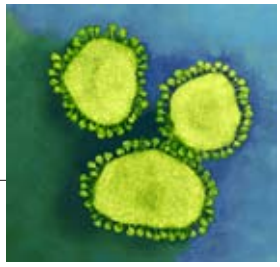

DR LINDA STANNARD, UCT/SPL

Coronavirus particles

Novel coronavirus: how much of a threat?

We know the questions to ask; we don't yet have many answers

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A third case of novel coronavirus (NCoV) infection was reported by the Health Protection Agency (HPA) on 15 February 2013, part of a family cluster of three cases in the West Midlands, England.[1] This means that 13 cases have been laboratory confirmed worldwide since September 2012. Four cases have been diagnosed in the United Kingdom, and seven patients, including one in the UK, have died.[2] The index patient in the recent UK cluster had travelled to Saudi Arabia and Pakistan in the 10 days before the onset of disease, whereas the second and third cases were family members who had not been abroad and probably acquired their infection after contact with the index case. The earlier UK case was a previously well adult transferred to intensive care in London from Qatar with severe respiratory illness in September 2012.[3] What have we discovered about this new pathogen from the few cases so far reported? Is this likely to represent a global public health threat akin to that from severe acute respiratory syndrome (SARS) coronavirus?

Human coronaviruses, first identified in the 1960s, are part of a diverse group of viruses found in humans and animals. In humans these RNA viruses typically cause respiratory illnesses ranging from the common cold, caused by a group of seasonal coronaviruses (229E and OC43), to the severe respiratory disease caused by the recently recognised SARS coronavirus responsible for the global outbreak in 2002-03.

The limited information we have indicates that person-to-person transmission is unusual

What can we say about the source of NCoV? Other than the patients who acquired the infection through contact with a confirmed case in the UK, all others became unwell in the Middle East, suggesting this region as the source, although the full geographical extent is unknown. Although NCoV is genetically similar to other coronaviruses present in bats,[4] the reservoir remains unknown, as does its route of transmission to humans and risk factors for human infection. One possibility is that the virus circulates in one or more animal groups and is transmitted intermittently to humans as a sporadic zoonotic infection. This could be by direct contact with the natural animal reservoir, by indirect transmission through an intermediate host, or through food or environmental contamination.

How is the virus transmitted and what is the spectrum of illness in humans? Might transmission be sustained in the human population with widespread asymptomatic infection or only mild symptoms, enabling the illness to go mostly undetected? And might the infection have been circulating undetected for some time? The limited information we have indicates that person-to-person transmission is unusual. The 13 recent cases were confirmed after the development of a diagnostic test in September 2012.[5] Five were sporadic, with no associated human cases. The remainder occurred in three clusters with limited chains of transmission: two cases in one cluster in an intensive care unit in Jordan,[6] and the others in two family clusters of three cases each in Saudi Arabia and the UK. Extensive follow-up of close contacts of the first patient diagnosed in the UK (HPA, unpublished data),[3] and of a patient transferred from Qatar to Germany,[7] detected no secondary cases using virological and serological endpoints.

What is the spectrum of illness? Evidence to date suggests that infection usually results in a severe illness. All but one of the 13 cases have been severe enough to require hospital admission and 11 have needed intensive care. Follow-up of close contacts of the index case in the recent UK cluster has identified a single case of a mild respiratory illness with detection of NCoV in sputum.[8] However, intensive clinical, virological, and serological follow-up of close contacts of two previous cases failed to find evidence of mild or asymptomatic infection.[3 7]

The World Health Organization has provided guidance on surveillance to detect possible cases of this novel virus.[9] Recognising such cases in the UK requires clinical and public health vigilance, combined with rapid microbiological investigation to rule out other causes and to confirm NCoV infection.[10] Patients need supportive clinical care. No recognised effective treatment is yet available, although possible interventions that need to be investigated in clinical trials include convalescent plasma from recovered cases, antiviral therapies used for other viral infections, or immune modulatory agents. Strict infection control needs to be rapidly instituted for confirmed cases to prevent onward spread, and close contacts need to be identified and followed up.[11] If respiratory illness occurs in the 10 days after last exposure in a close contact the contact should be isolated and investigated urgently for NCoV infection.

Further work needs to be undertaken rapidly to fill the gaps in our knowledge of the clinical, virological, and epidemiological aspects of this infection, as world experience remains limited. In view of the apparent high case fatality ratio and lack of known treatments, confirmed cases need to be studied in detail to gain a better understanding of the natural course of infection in human hosts, the potential therapeutic options, and the nature of genetic variation between different strains to help piece together the origin of this viral infection. Although resource intensive, close follow-up of cases and contacts is needed to help understand the spectrum of illness and risk of infection in those exposed. Work is also needed to identify potential reservoirs of infection, risk factors for infection, and the prevalence of NCoV infection among people with acute respiratory illness in the Middle East and elsewhere. The question of whether this is a new virus in humans, or a newly recognised virus infection that has been undetected for some time, should also be investigated.

It is not yet clear whether a low level of sporadic infections with occasional limited person-to-person spread will continue to occur, or whether case numbers will build as a prelude to sustained transmission in the human population. The global experience of SARS is a salutary reminder of the devastation that can result from a newly emerging infection capable of human-to-human transmission. Improvements in diagnostic technologies and application of infection control lessons learnt from SARS have contributed to the response to NCoV infection. Until answers to some of these questions are available it is essential to maintain the current high level of vigilance for cases, to intensively investigate all cases and their contacts, and to share the information rapidly.

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Researchers should consider the novel approach proposed by Wennberg and colleagues to separate the effect of supply from need

Making the best use of administrative data

The difficulty of teasing out demand and supply

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Making better use of routine administrative data is becoming an ever more integral part of delivering higher quality more efficient healthcare. Routine data are useful when evaluating complex interventions related to the management of patients with long term conditions, which need continuous monitoring and refinement.[1] Other applications of routine data are predictive models, which have been developed to identify patients at high risk of future adverse events.[2] Finally, payment mechanisms almost inevitably use (and generate) routine data, and routine data are the basis for many performance indicators.[3]

Problems with routine data are well known. They often do not tell us everything we need to know (for example, wider determinants of health), they rarely capture the direct views of patients and do not always correlate well with what patients tell us,[4] they vary in quality and depth of data, and they can be "gamed."[5] Furthermore, as pointed out in a linked paper by Wennberg and colleagues, it can be challenging to separate out healthcare need from supply in analyses of routine data.[6] This problem of judging needs through the lens of diagnosis markers in routine data can be described simply. If measures of healthcare needs are built up from the diagnoses recorded in hospital datasets, a diagnosis can be present only if the patient has been to the hospital. The propen- sity to admit coupled with the intensity with which doctors observe and diagnose patients differs between areas, leading to a distorted picture of healthcare needs. This is not a new problem but has been at the heart of debates about funding for many years.[7]

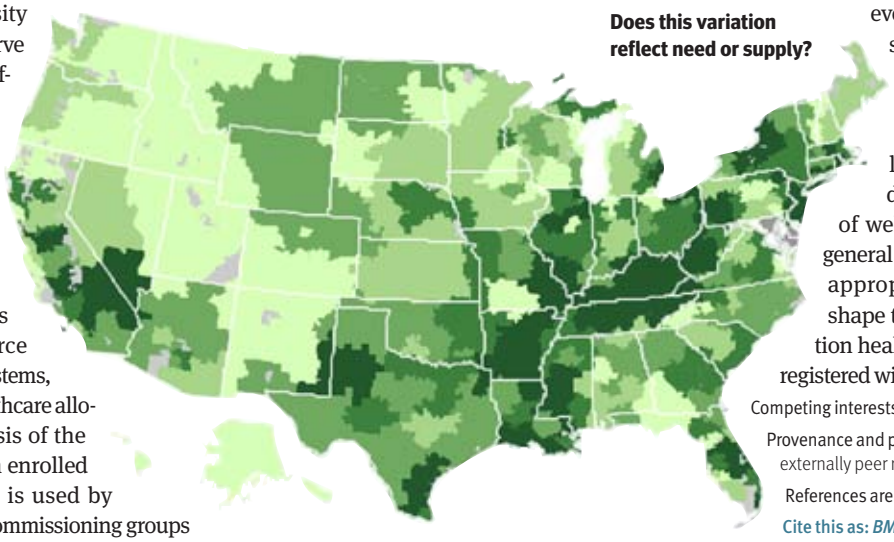
The phenomenon has implications for resource allocation in capitated systems, where purchasers of healthcare allocate funding on the basis of the estimated needs of each enrolled person. Such a system is used by budget holding clinical commissioning groups in England, health insurance plans in the Netherlands, and Medicare Advantage plans in the United States, among others. In these systems, stripping out the effect of supply from estimates of need is important, if payments are to reflect need rather than patterns of service use (because of the potential to reward areas with modest level of need but inappropriately high levels of service use in the past). This problem, just like other problems with routine data, is well known, and there are ways to try to deal with it. For example, in the person based resource allocation (PBRA) formula that guides resource allocation for general practices in England, the effects of supply variables at the level of the individual were "frozen out" of the eventual allocations.[8]

Wennberg and colleagues assert that measures of healthcare need lack validity if they do not explain variations in age, sex, and ethnicity adjusted mortality rates between regions. When they tested three common methods of estimating need from diagnosis fields in Medicare claims data, they found that they explained only 10-12% of the variation at the region level. This approach assumes that needs are reflected in mortality rates, which brings us to the thorny question of what we mean by "need." A formula for funding hospital care like PBRA should presumably reflect those elements of need that can be dealt with by hospital care, and we know that patterns of mortality are influenced by many factors outside the hospital.[9]

Nevertheless, researchers should consider the novel approach proposed by Wennberg and colleagues to separate the effect of supply from need. This was based on taking the number of times patients were seen by doctors in their last six months of life as a proxy for observation intensity in any one region. When they adjusted their estimates of need for this quantity, the proportion of mortality explained jumped to 21-24%. This is an interesting approach, but the proxy cannot be a perfect measure of observation intensity, because patients in the last six months of life will have varying levels of need and variable supply of alternatives to Medicare. Furthermore, the configuration of palliative care may not reflect how care services are delivered for other population groups.

The challenges of teasing out demand and supply mean that we need to test the value of this approach in other datasets. The approach also needs to be compared with existing methods, such as the "freezing" method used by PBRA, to see which is best at reducing bias in the estimates. Furthermore, validation requires more criteria, including those measured at different levels (such as the level of the organisations to which capitated payments are made).

Meanwhile, these challenges are not a reason to stop using routine data. All datasets have their drawbacks, and resources need to be allocated somehow. As Wennberg and colleagues suggest, we can get smarter in the way that we use the data. Ultimately, though, fancier statistical methods won't solve the problem of datasets not telling us everything we need to know. The solution should involve putting more effort into collecting outcomes data from patients routinely, as well as safe data linkage.[10 11] The United Kingdom has the huge advantage of well established computerised general practice records, which, given appropriate safeguards, can help shape the ways we consider population health in future, at least for those registered with general practitioners.



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A concern that can be plausibly doubted or denied carries no legal liability, whereas one that gives rise to serious consideration… leaves the door wide open to litigation

GLP-1 based agents and acute pancreatitis

Drug safety falls victim to the three monkey paradigm

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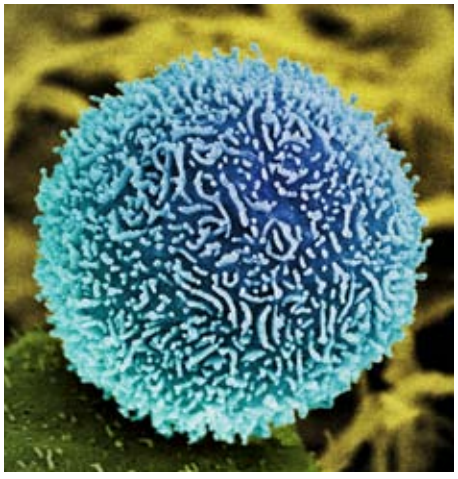
Investment companies knew that the Food and Drug Administration safety database carried a signal for acute pancreatitis with the antidiabetic drug exenatide (a glucagon-like peptide 1 (GLP-1) agonist) in 2006, a year before the agency alerted doctors[1]—a curious reflection on the way we mix business with medicine. The signal had reached astronomical dimensions (more than 10 times that in control drugs) by 2011 and has accelerated since.[2] Furthermore, all GLP-1 based agents that have been on the market for more than two years have also generated a signal for acute pancreatitis, suggesting a class effect.

The regulators asked companies to provide more data, and companies have responded with studies showing that acute pancreatitis is more common in diabetes than previously thought and that clear evidence of an increased risk of pancreatitis with GLP-1 based treatments is lacking.[3] Warnings on the label notwithstanding, the industry has been able to maintain that the problem does not exist—and has a huge incentive to do so.

This is no longer tenable. A report in *JAMA Internal Medicine* describes a case-control study of more than a million people with diabetes, which yielded 1269 cases of acute pancreatitis in people aged 35-64 years using exenatide or sitagliptin, and an equal number of cases in people on non-GLP based antidiabetes drugs. However, after multiple adjustments, current users and recent users (one month to two years) of GLP-1 based treatments had a twofold increased risk of acute pancreatitis (adjusted odds ratio 2.24 (95% confidence interval 1.36 to 3.68) for current use and 2.01 (1.27 to 3.18) for recent use) compared with those taking non-GLP based antidiabetes drugs.[4] A company sponsored study had found an increase in episodes of pancreatitis in recent users of exenatide, but it discounted this because those affected were no longer taking the drug.[3]

Should we be worried about this? Very much so. GLP-1 is a pleiotropic agent that has many actions apart from its therapeutic effects in promoting insulin secretion, inhibiting glucagon release, delaying gastric emptying, and reducing appetite. It also interacts, for example, with receptors in the heart, kidneys, thyroid, and exocrine pancreas. Furthermore, GLP-1 is a very short acting peptide, and the consequences of long term pharmacological stimulation in humans are unknown. GLP-1 promotes cell replication in some tissues, and it was hoped that it would promote pancreatic β cell regeneration until this action was found to be restricted to immature rodents. This may have distracted attention from the fact that it also stimulates pancreatic duct cells to divide, regardless of age. It has been known for more than a decade that animal pancreas tissue increases in weight on exposure to GLP-1 and that this must represent overgrowth of the exocrine pancreas.[5]



STEVE GSCHMEISSNER/SPL

Pancreatic cancer cell: all forms of pancreatitis predispose to carcinoma of the pancreas

Further observations in experimental animals prompted the hypothesis that overgrowth of pancreatic duct cells produces occasional obstruction of the smallest ducts, with the potential to cause subclinical pancreatic inflammation in many users and full blown acute pancreatitis in rare instances.[6] Acute pancreatitis is unpleasant enough, but the major concern relates to subclinical inflammation of the pancreas. Postmortem analysis of humans exposed to GLP-1 based agents has yet to be reported, but it is well known that concentrations of pancreatic enzymes rise in animals and humans taking GLP-1 based drugs compared with other treatments for diabetes. Companies have modestly omitted these data from their published trials, sometimes with the comment that no "clinically significant" changes were seen. As a result, there is only one formal description of the phenomenon—from an independent group—in the literature.[7] Subclinical increases in enzyme concentrations may not prove subclinical pancreatitis, but they provide no reassurance about its absence.

One reason why the merest possibility of pancreatitis has been contested so vigorously is that all forms of pancreatitis, clinical or subclinical, predispose to carcinoma of the pancreas. The harbingers of this unpleasant cancer, known as pancreatic intraepithelial lesions, are widely present as potential seeds of cancer in the adult population. These lesions carry the GLP-1 receptor, as do pancreatic carcinomas. Increased reporting of pancreatic cancer was independently noted in both the FDA and German regulatory databases.[2 8]

Why have the companies been so slow to respond to this threat? Because of the "three monkey paradigm," which operates as follows. Companies are legally responsible for monitoring the safety of their own products, but self evidently cannot be held responsible for tackling a safety concern that does not exist. A concern that can be plausibly doubted or denied carries no legal liability, whereas one that gives rise to serious consideration (even in internal emails, which are discoverable) leaves the door wide open to litigation. Inviting companies to monitor the safety of their own products thus provides them with the strongest possible incentive for failing to do so, an instance of the law of unintended consequences. The three monkeys, who neither hear nor see nor speak, have been allowed to flourish at the heart of our system for protecting the public. The regulators should not follow this example.

Competing interests: I have provided expert testimony in litigation concerning exenatide.

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References are in the version on bmj.com.

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TOO MUCH MEDICINE

Overdiagnosis may be the norm rather than the exception

Winding back the harms of too much medicine

Registration is opening and abstracts closing soon for our "Preventing Overdiagnosis" conference

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Distinguishing the sick from the healthy has always been a fundamental challenge for medicine. A chief concern has been to guard against missing disease, with the focus on problems of underdiagnosis and undertreatment. Yet with the modern technological expansion of healthcare in rich developed nations, sceptical voices have long warned of the flipside—too much medicine.[1 2] Mounting evidence about the threat to human health from overdiagnosis,[3] and the harms and waste from unnecessary tests and treatments,[4 5] now demand that we meet one of this century's key challenges: how to wind back medical excess, safely and fairly.

In 2002 the *BMJ* published a theme issue called "Too Much Medicine?" with articles on the medicalisation of birth, sex, and death, among other aspects of ordinary life. Its opening editorial wondered whether doctors could become pioneers of de-medicalisation, handing back power to patients, resisting disease mongering, and demanding fairer global distribution of effective treatments.[6] A decade later, as data on overuse and overdiagnosis mount,[3] the *BMJ* announces a "Too Much Medicine" campaign—this time without the qestion mark (www.bmj.com/too-much-medicine).

Through the campaign the journal plans to work with others to highlight and contribute to the growing evidence base on overdiagnosis and overtreatment. In October last year, for example, a major inquiry cited evidence based estimates that as many as one in five women given a diagnosis of breast cancer as a result of screening would not have been harmed by that cancer.[7] In December, the chair of the DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders*, fourth edition) task force warned of the potential for "massive overdiagnosis and harmful overmedication" with increasing expansion of the definitions of mental disorders—for example, turning the physical symptoms of cancer or heart disease into a mental disorder "somatic symptom disorder"—in the forthcoming fifth edition of the manual.[8]

Data suggest that overdiagnosis exists to some extent across a range of common conditions, including prostate and thyroid cancers,[3] asthma, chronic kidney disease, and attention deficit hyperactivity disorder.[9] Indeed, overdiagnosis may be the norm rather than the exception. This matters because once people are labelled with a diagnosis, a cascade of medical, social, and economic consequences follows—some of which are permanent. The medical label and the ensuing treatment take an emotional and financial toll on the person, while also costing the health system.

Importantly, overdiagnosis and underdiagnosis coexist in many healthcare settings, both rich and poor. Concern about overdiagnosis of chronic kidney disease in older people exists alongside evidence that some groups disproportionately experience avoidable harm from serious kidney disease.[10] Because of this and other uncertainties, it will not be easy to communicate effectively about overdiagnosis with professionals and the public. The concept is unfamiliar and counterintuitive to many people.

The *BMJ*'s campaign must be seen as part of a larger effort to combat over-medicalisation, including the "Choosing Wisely" campaign, run by a coalition of US medical specialty societies to combat the overuse and misuse of tests[11]; the recent Avoiding Avoidable Care conference, run by the Lown Cardiovascular Research Foundation (http://avoidablecare.org/); and the second Selling Sickness conference, held last week in Washington, DC, which brought together academic critics of the drug industry, health reformers, consumer advocates, and journalists (http://sellingsickness.com/). Although each has specific concerns and recommendations, all share the same goal: implementing practices that help people who are sick and do not harm those who are well.

In addition, the *BMJ* is a partner in an international scientific conference on preventing overdiagnosis, to be held in September this year in Hanover, New Hampshire, USA. It is hosted by the Dartmouth Institute for Health Policy and Clinical Practice, and held in concert with Bond University in Queensland, Australia, and Consumer Reports in New York. The conference seeks to bring together researchers and policy makers, to advance the science of overdiagnosis, and develop ways to better communicate about this "modern epidemic." Abstract submissions close on 15 March, and registration is now open at www.preventingoverdiagnosis.net.

Dartmouth is a natural home for the conference, with its reputation for documenting variations in practice[12] and investigating overdiagnosis.[3] Similarly, the leading US not-for-profit consumer organisation, Consumer Reports, is a natural partner, producing rigorous information for patients and the public about the benefits and harms of treatments and technologies (www.consumerreports.org/health/home.htm). Although mainly a scientific gathering, the September conference hopes to spark a broader conversation with a wider range of players from industry, academia, policy making, professional associations, and citizens' groups.

As part of the campaign the *BMJ* will produce a theme issue in early 2014, featuring the best papers from September's conference. The *BMJ* and Consumer Reports will also soon begin a series of articles, with versions for clinicians and consumers, on how the expansion of disease definitions is contributing to overdiagnosis. The series will feature common conditions, including pulmonary embolism, chronic kidney disease, and (pre) dementia. Underscoring the need for caution, each article will feature a limitations section, highlighting the controversies and caveats accompanying this evolving and complex science.

Like the movements of previous decades that have advanced evidence based medicine and quality and safety in healthcare, the movement to combat medical excess in wealthier nations embodies a much older desire to avoid doing harm when we try to help or heal. Such efforts are made more urgent by escalating healthcare spending. Winding back unnecessary tests, diagnoses, and treatments will not only protect individuals from harm, it will help society focus on the broader issues of health in ways that are economically sustainable.

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