How well is the UK managing the influenza A/H1N1 pandemic?

Pretty well, and it's an important rehearsal for a more lethal one

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News headlines this week have certainly raised anxiety over the influenza A/H1N1 (swine flu) pandemic in the United Kingdom, with reports of 29 deaths to date since the national epidemic started in late April, and one of the dead being a 6 year old girl with apparently no pre-existing medical conditions. NHS Direct telephone lines have been swamped in recent days as the epidemic continues to expand and mortality rises.

How serious is the UK epidemic, and what are the likely trends over the coming months as autumn arrives? General practice consultation rates in England for patients presenting with flu-like illness have increased and are now above the threshold for normal seasonal flu activity. The 5-14 year olds remain the age group predominantly affected, with London and the West Midlands being the worst affected regions. Mortality among clinical cases with confirmed influenza A/H1N1 infection is currently between 1 per 200 and 1 per 400. This is a higher figure than that typically seen with seasonal flu, but the true figure per case of infection will be much lower because of a high prevalence of mild symptoms not captured in the current reporting system. Many biases affect these estimates, as reported in the linked article by Garske and colleagues.[1] More detailed retrospective household studies are needed now, with serology to ascertain infection and morbidity. These are planned to take place in the coming months.

The most surprising feature of the UK epidemic is its continued growth through June and July, when seasonal flu normally drops to very low levels. This is apparent not only in the UK, but also in the United States and Canada. The high numbers of cases in these countries, relative to other regions (except South America—the epidemic is believed to have originated in Mexico[2]), probably says more about the efficiency of public health reporting systems and diagnostic capabilities than regional differences in transmission. At present, 135 countries have reported confirmed cases of swine flu; many more probably have epidemic spread but lack reporting systems to capture incidence, morbidity, and mortality.

The reasons for epidemic expansion in the summer months in northern hemisphere countries are not well understood. The observed trends may change views about the relative importance of herd immunity and seasonal factors such as humidity, temperature, and human behaviour as determinants of the incidence of flu. The high susceptibility of human communities to the new virus may imply that seasonal fluctuations in transmission are insufficient, in a fully naive population, to drive the reproductive number (average number of secondary cases generated by one primary case[3]) below unity in value, as normally happens in a partially susceptible population exposed to a virus closely related to that circulating in the previous year. The onset of school holidays in the northern hemisphere should decrease transmission markedly, but the epidemic is likely to be sustained over August before it starts to expand vigorously again in the autumn, as children reassemble for school. Health services may well be stretched in the UK, as will the economy, owing to high rates of absenteeism from work.

How well prepared was the UK for this current outbreak, given the intense planning that previously took place for the management of a pandemic of the much more lethal, but much less transmissible, H5N1 bird flu virus? Government machinery swept into action quickly in late April, and the assembly of advisory groups for COBR (Cabinet Office Briefing Room) meetings with ministers and civil servants worked well. The UK was well placed in terms of stocks of antiviral drugs and with respect to preorders of a vaccine specific to an emergent pandemic flu strain. Supplies of the vaccine will be available in early autumn, and the government aims to vaccinate most of the population. Plans are currently being drawn up to determine the priorities for immunisation as stocks build up in the autumn months.

Antiviral drugs were used to good effect in the early phase of the UK epidemic as prophylaxis, in a containment strategy targeted at contacts within households, schools, and work settings. Retrospective analyses tentatively suggest that this strategy slowed transmission, but as suggested by previous mathematical analyses of flu spread, this delayed epidemic growth only by a few weeks.[4] Now the strategy has shifted to the treatment of cases and those most at risk of serious morbidity from infection after contact with a case. This change in treatment strategy is sensible and conserves the supply of antiviral drugs for those most in need as the epidemic expands in the coming months.

What could be improved? In common with other

countries' pandemic plans, those in the UK lacked detail in many areas. These included the logistics of drug delivery, how to ensure and monitor good compliance to the prescribed antiviral treatment course, the provision of sufficient diagnostic services, data capture and reporting in primary and secondary care settings and on a national scale, monitoring viral evolution, clinical case definition, and the setting of priorities for treatment plus vaccination. Technologies to help in protection and containment such as face masks and rapid diagnostic tools did not receive high priority in planning, but these tools would be of great value within healthcare settings in rapidly expanding flu epidemics.[5]

In the early stages, some media websites provided much more useful information to the public in tracking the unfolding epidemic than official government sites. This has now been rectified. The UK performed much better than most, particularly the US, where in the early stages of epidemic growth, case information on attack rates and morbidity was released slowly, despite high case numbers. UK scientists, in collaboration with Mexican colleagues, were the first to publish epidemiological analyses of the emerging epidemic.[2]

The UK's plan to capture details of the first 100 cases to inform policy formulation worked in part. Guidelines for use in clinical settings on the information that needs to be gathered and on the procedures needed to follow-up cases and contacts, to obtain viral isolates and serum or saliva, and to track the course of viraemia in treated and untreated patients all need to be improved. The Health Protection Agency has performed sterling work under a rapidly expanding case load. However, improvements could be made to ensure better communication between groups within the agency; better and more rapid access to data; and better use and integration of resources from universities, which have much scientific, epidemiological, and clinical expertise, plus access to facilities. Use of such academic resources could greatly facilitate rapid epidemiological analyses, through developing clear criteria for clinical case definition, defining guidelines for when to use antiviral drugs, and monitoring viral evolution—especially in the context of drug resistance and varied compliance to prescribed drug regimens.

Overall, much has been learnt in the past few months from what, thankfully, still seems to be mild flu in most of those infected. In many ways, the emergence of influenza A/H1N1 has served as an important rehearsal worldwide for a future and perhaps much more lethal pandemic. A thorough and frank "lessons learnt" exercise must be performed once the epidemic wanes.

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Overdiagnosis and mammography screening

The question is no longer whether, but how often, it occurs

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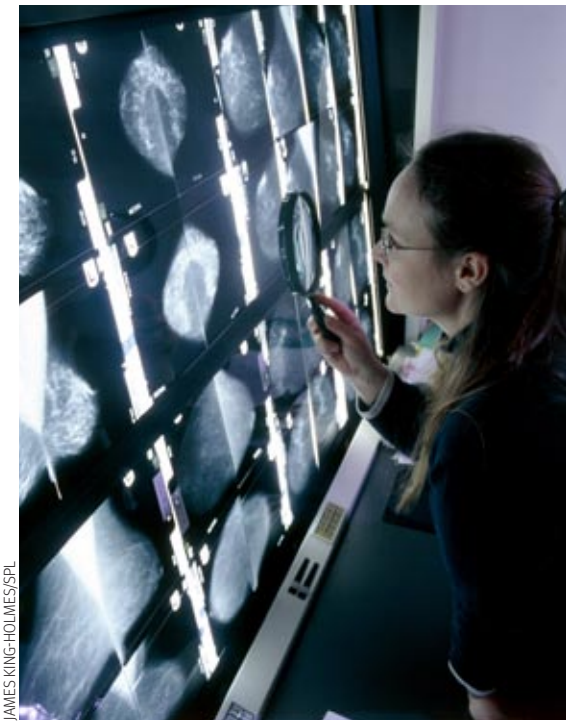
The NHS recently scrapped its leaflet inviting women to undergo mammography in response to criticisms that it failed to mention the major harm of screening—overdiagnosis.[1] In the linked systematic review, Jørgensen and Gøtzsche provide evidence that screening has led to overdiagnosis of breast cancer not only in the United Kingdom, but also in Canada, Australia, Sweden, and Norway.[2]

Overdiagnosis refers to the detection of abnormalities that will never cause symptoms or death during a patient's lifetime. Overdiagnosis of cancer occurs when the cancer grows so slowly that the patient dies of other causes before it produces symptoms or when the cancer remains dormant (or regresses). Because doctors don't know which patients are overdiagnosed, we tend to treat them all. Overdiagnosis therefore results in unnecessary treatment.

With the advent of widespread efforts to diagnose cancer earlier, overdiagnosis has become an increasingly vexing problem. Overdiagnosis is a widely recognised problem in prostate cancer screening, and it has also been reported in other cancers, including neuroblastoma, melanoma, thyroid cancer, and lung cancer. Some degree of overdiagnosis is likely to be the rule rather than the exception in cancer screening.

Jørgensen and Gøtzsche's results are consistent with a growing body of observational evidence that screening mammography is associated with sustained increases in the incidence of breast cancer in women of screening age, with little or no subsequent decrease in incidence in older women.[3-6] One cohort study concluded that some invasive breast cancers detected by screening must spontaneously regress.[7]

But legitimate questions can always be raised about the role of confounding in inferences based on observational data. The most compelling evidence to date, therefore, is the long term follow-up of the randomised controlled trial by Zackrisson and colleagues that was published in the *BMJ* three years ago.[8] At the end of the 10 year trial, 150 more women were diagnosed



JAMES KING-HOLMES/SPL

with breast cancer in the mammography group than were diagnosed in the control group. Such an excess is expected—for mammography to work, it must advance the time of diagnosis for some women and lead to more women being diagnosed in any discrete period after its initiation. The researchers followed the women for another 15 years, during which time both groups received the same amount of mammography, so that cancers in the control group would have had the chance to "catch up." But after a total of 25 years, there were still 115 extra women diagnosed in the group originally randomised to mammography. Unless mammography itself causes cancer, this persistent excess is strong evidence for overdiagnosis.

The question is no longer whether overdiagnosis occurs, but how often it occurs. Jørgensen and Gøtzsche conclude that about one in three of all breast cancers detected represent overdiagnosis. The corresponding number from Zackrisson and colleagues' study is one in six.[9] But these may not be the most useful numbers from the users' perspective.

Mammography is one of medicine's "close calls"—a delicate balance between benefits and harms—where different people in the same situation might reasonably make different choices. Mammography undoubtedly helps some women but hurts others. No right answer exists, instead it is a personal choice.

Draft balance sheet for screening mammography in 50 year old women*

Credits	Debits
woman will avoid dying from breast cancer[10]	2-10 women will be overdiagnosed and treated needlessly
	10-15 women will be told they have breast cancer earlier than they would otherwise have been told, but this will not affect their prognosis
	100-500 women will have at least one "false alarm" (about half of these women will undergo a biopsy)

*For every 1000 women undergoing annual mammography for 10 years

To inform that choice, women need a simple tabular display of benefit and harms—a balance sheet of credits and debits (see table for a draft version).

The cumulative risk of a false positive mammogram result varies widely on the basis of geography, but women largely accept this risk.[11] We do not know how women feel about being diagnosed at a younger age without this influencing their prognosis (those destined to die still do, those destined to survive would have done just as well if diagnosed later).

The information that will probably influence most women's choice will be data on the trade-off between the number of deaths from breast cancer avoided and the number of cancers overdiagnosed. More research is needed to confirm or dispute this assertion and to determine how sensitive women's choices are to various estimates of the trade-off.

Equally important are the estimates themselves. Zackrisson and colleagues reported 62 fewer deaths from breast cancer and 115 women overdiagnosed—a ratio of one death avoided to two women overdiagnosed. Recently, Gøtzsche and colleagues argued in the *BMJ* that the ratio is one to 10.[12] For many women, the tipping point may be within this range. Careful analyses that explicitly lay out their assumptions and methods, which will improve the precision of these estimates, are sorely needed.

Finally, researchers need to do more than just describe the problem, they need to work towards mitigating it. The amount of overdiagnosis is a function of the mammographer's threshold to recommend biopsy. The time has come for a randomised controlled trial to test higher thresholds, such as only recommending biopsy for breast masses larger than a certain size.

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Inappropriate referencing in research

Has serious consequences, and the research community needs to act

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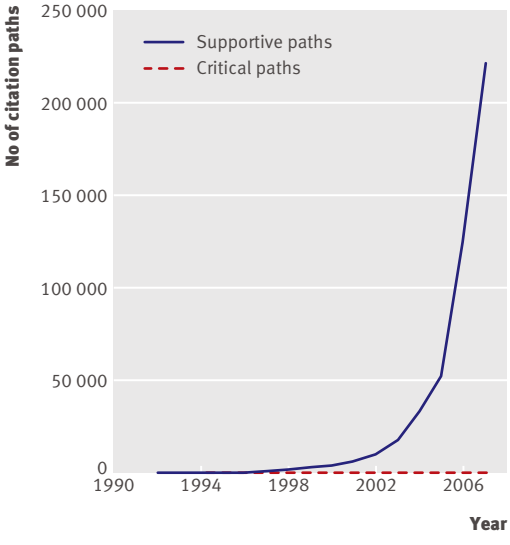
During the preparation and writing of manuscripts, protocols, grant submissions, technical reports, and conference abstracts, authors must consider carefully the selection, completeness, and appropriateness of the articles referenced. Improper citation is not a benign practice; adequate and accurate citation is a necessity of scientifically and methodologically sound research. Rather than treating citation errors in a particular journal article as isolated incidents, we must appreciate that such errors can be replicated in further articles and, therefore, cause considerable damage over time. Incorrect information can be promoted, alternative evidence ignored, and redundant research undertaken following inappropriate use of references, impairing scientific progress and affecting patient care.

In the linked study, Greenberg illustrates a number of serious consequences of inappropriate or inaccurate citation of published scientific work. Greenberg tracks the citation history of the hypothesis that β amyloid is "produced by and injures skeletal muscle fibres of patients with inclusion body myositis".[1] He concludes that the publication and respective citation history for this hypothesis offers empirical evidence that inappropriate or inaccurate citation can cause serious distortions, including bias, amplification, and invention. Erroneous and unfounded claims can be perpetuated, which sets back real scientific progress and has direct implications on how patients are treated (see figure).

A clear message emanating from Greenberg's work is that investigators have an obligation to critically appraise existing evidence and develop their own interpretation of the results of individual studies. Although explanations provided in published studies are helpful and insightful, we must not rely solely on the word of the authors. In articles referencing a previous study, the interpretation of this work provided in the text may be insufficient. Although tempting, we must not rely on descriptions provided by authors citing a primary paper, who may lack or be ignorant of primary results. Ideally, the data that form the basis of claims in a paper should be replicated from the primary source, either in the article or an appendix. As imparted by teachers and mentors in research, we as authors must always address the scientific and methodological limitations of our findings. Incorporation of these limitations should accompany any future citation, as their absence can bias interpretation.



Growth over time of citation paths which supported, and those which criticised or refuted, the claim that β amyloid and its precursors are abnormally and specifically present in inclusion body myositis muscle fibres[1]

Greenberg also shows the fundamental need for systematic reviews in all types of research. By selectively citing studies or unsystematic reviews that suit a particular hypothesis, a bias so serious that the recommendations put forth are erroneous can be introduced. We can no longer continue to choose and selectively report work that does not represent the spectrum of available evidence.

Traditionally, the majority of systematic reviews have concentrated on summarising clinical evidence of effectiveness or efficacy provided by randomised clinical trials conducted in humans. The utility of systematic reviews extends well beyond questions of clinical effectiveness. Through a systematic and transparent review process—including literature searches, eligibility criteria, and quality appraisal—they provide a less biased presentation and summary of the evidence base than traditional narrative reviews.

Indeed, basic research would also benefit from systematic reviews to justify and support proposed hypotheses and respective methods. Problems such as inadequate sample size, poor study design, lack of blinding, and lack of randomisation hold true for animal research as well as for clinical research. Although the methods and protocols for conducting systematic reviews in basic research lag far behind those for clinical research in humans, these limitations do not preclude their conduct.

Some may argue that Greenberg's research assesses but a single example of improper citation. Further research investigating the extent and impact of citation bias is warranted and extensive preventive measures to ensure proper procedures are followed should be introduced. We do not require a body of evidence that demonstrates wrong doing; instead, we need assurances that biases are minimised in the preparation of scientific documents.

First, for any grant proposal, investigators must incorporate a systematic review to justify their proposed

hypothesis and objectives. Investigators can either integrate a published systematic review or, if absent, undertake their own. Doing so at least ensures that the proposed hypothesis is relevant; the methodological and scientific limitations and strengths of previous research are considered; all previous evidence is weighed and incorporated; and a transparent path of literature review is provided to peer reviewers and non-peer reviewers.

Currently, certain grant organisations strongly encourage a systematic review for all clinical trial proposals.[2 3] A systematic review should, however, be required for any research protocol, regardless of hypothesis, study design, or types of participants. This measure requires a large and, for some, uncomfortable step forward, but it is a necessary step. Indeed, the need for systematic reviews extends beyond the issue of citation bias.

Second, journals should require corresponding authors to formally acknowledge that they take responsibility for the appropriateness and accuracy of their manuscript's reference list. This measure should raise awareness of the seriousness of improper citation rather than be a legal requirement. The acknowledgment would be comparable to the current practice at journals for authors to pronounce their roles in data acquisition, statistical analysis, drafting of the manuscript, and study interpretation. Compared to the current situation in which citation review is left only to the editorial office, a simple check box could ensure that authors are accountable for the completeness, accuracy, and interpretation of references. In turn, this measure could produce stronger manuscripts that are less prone to citation bias and its deleterious downstream effects.

Research hypotheses require robust evidence along with a strong rationale, and health professionals require a complete and balanced account of the evidence base to better guide patient care. Scientific progress is set back by faulty hypotheses and redundant research that is propagated by selective and erroneous citation practices. The research community must attend to the issue of citation bias with some urgency.

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3 Medical Research Council. Trial grant information. www.mrc.ac.uk/Utilities/Search/MRC001732.

Why is mortality from coronary heart disease in young adults no longer falling?

Social inequalities must be tackled, as well as risk factors

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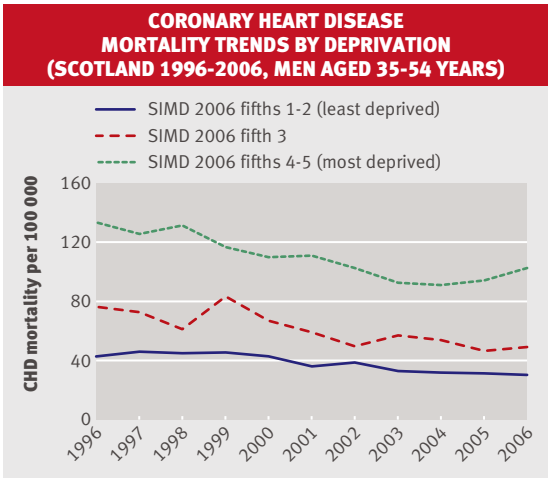
In the linked study, O'Flaherty and colleagues examine trends in mortality from coronary heart disease in Scotland according to age and deprivation, from 1986 to 2006.[1] The study adds to these authors' previous work on the role of risk factors and advances in medical care in explaining the decline of mortality from coronary heart disease in several countries. The study shows that mortality from this disease has flattened in younger adults (age 35-54) in the most socially deprived groups. This work shows how changes in population levels of traditional risk factors have led to the impressive decline in mortality from coronary heart disease in recent decades.[2]

Mortality has fallen and age standardised rates are down in all social groups. This is good news, but, on the negative side, the favourable trends are flattening in younger men and perhaps women, although the authors caution not to overstate the importance of these changes. This is an example of the usefulness of examining age specific rates before naively applying age standardisation. A similar levelling of mortality from coronary heart disease in younger people has been seen in other developed countries such as Australia[3] and the United States.[4] When O'Flaherty and colleagues examined age specific mortality by deprivation score, they found that mortality was decreasing at all ages in almost all social groups. They also found that relative inequalities were reasonably flat but absolute inequalities decreased in most age groups in men and women, although they do not present data on changes in absolute inequality.[1] What is most worrying is that the slowing of improvements at younger ages is confined to the most deprived groups of young men and women, as has been reported elsewhere.[5 6] Why are the most deprived young adults in Scotland not sharing the benefits seen by others?

Risk factors for coronary heart disease follow strong social patterns, and differential changes in risk factors are a plausible explanation. Yet the evidence does not seem to support this argument. Although at a national level improvements in many risk factors (cholesterol, body mass index, blood pressure, diet, physical activity, and smoking) in England corresponded to an overall decline in mortality from coronary heart disease, slight changes in the prevalence of risk factors leading to a less marked social gradient did not tally with an increase in inequalities in mortality.[7] A similar decoupling of traditional risk factors (total serum cholesterol, hypertension, and smoking) from mortality for cardiovascular disease



Coronary heart disease mortality in men aged 35-54 in the two most deprived fifths decreased between 1996 and 2004 in Scotland. However, the annual change between 2004 and 2006 was not significantly different from 0%

was seen in Finland, where declining mortality in different social groups can no longer be explained by changes in risk factors, with changes in risk factors underestimating the extent of this decline.[8] Possible reasons for the lack of correspondence between the two include uncertainty about the time lag between changes in risk factors and changes in mortality or social patterns in the use of secondary prevention and invasive cardiac procedures.

But coronary heart disease is not the only cause of death to show changing patterns over recent years. In Scotland the decline in mortality in men under 60 slowed down in the 1990s, with overall death rates starting to increase in men aged 15-44.[9] Such changes may reflect slowing declines in death from cardiovascular disease but have largely been driven by increases in suicide and mortality associated with the use of alcohol and drugs. Socioeconomic inequalities in mortality have increased for many causes other than cardiovascular disease in both sexes,[10 11] and these causes do not share the same risk factors. So any change in cardiovascular risk factors responsible for increasing inequalities in mortality from coronary heart disease must have been accompanied by similar changes in risk factors for other causes of death.

Another possible explanation for changes in the patterning of social inequalities is that the axis of inequality itself has changed. In O'Flaherty and colleagues' study, which uses an area based measure of deprivation, this could result from increasing polarisation (where the more deprived areas contain a greater concentration of deprived people, possibly because of selective migration) or increasing absolute differentials (the poor becoming poorer).[1] For an individual measure such as education the meaning or quality of different lengths of education may have changed over time.[10]

O'Flaherty and colleagues' study indicates that the levelling of mortality from coronary heart disease in young adults cannot be tackled without improving social inequalities. It may be that this can be achieved solely through modifying risk factors; although the link between risk factors and cardiovascular mortality has weakened, it still seems to be stronger for lower socioeconomic groups.[8] However, deliberate interventions to reduce inequalities in health through modification of major risk factors have had limited success to date. The alternative is to tackle the social inequalities themselves—unequal distribution of power, money, resources, and life chances.[12] Although not a quick fix solution, if it works then policies to reduce social inequalities will ultimately reduce inequalities in health associated with all causes that manifest as social gradients and not just coronary heart disease.

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