thebmj.com Find out more about the statins review at thebmj.com/statins

Risks in the balance: the statins row

Nigel Hawkes asks where *The BMJ*'s correction of two articles leaves patients and doctors

Imagine, if you will, a patient newly prescribed a statin by his general practitioner: let's call him Mr Lowrisk. It is Thursday 15 May, and as Mr Lowrisk sits down to breakfast the *Today* programme on BBC Radio 4 is broadcasting a discussion about the risks and benefits of statins. He listens carefully—a golf partner has warned him that statins can make your muscles ache. Defending statins, Rory Collins, an Oxford professor, asserts confidently, "There is a very, very low risk of muscle problems," a reassuring message for Mr Lowrisk. On his way to work he picks up his prescription, and at coffee time he reads the patient information leaflet.

To his surprise, listed under common side effects that may affect "up to one in 10 people" are joint pain, muscle pain, and back pain. "But I thought that professor said there was a very, very low risk of muscle problems," he mutters. Mr Lowrisk is confused. The manufacturers seem to be owning up to a side effect that the Oxford professor said barely even existed.

This vignette, oversimplified as it may be, encapsulates an argument over the risks and benefits of statins that has been raging ever since *The BMJ* published two articles on the subject in October last year.[1 2] The reputation of the journal has been called into question; so has that of the authors responsible, charged by Collins with deliberately misconstruing the evidence and unfitted, in his view, from ever contributing to the journal again. Comparisons have been drawn, again by Collins, with the scare over the measles, mumps, and rubella vaccine, in which parents were discouraged from getting their infants vaccinated by false evidence linking MMR to autism. "It is a serious disservice to British and international medicine," he told the *Guardian*, adding in reference to the MMR scare: "I would think the papers on statins are far worse in terms of the harm they have done."[3]

Comparisons have been drawn by Collins with the scare over the MMR vaccine

Calls for retraction

Collins's complaint was that the two articles exaggerated the harms of taking statins and as a result concluded that the drugs should not be prescribed to people at low risk of cardiovascular disease, like our imaginary golfer. Collins called for the articles to be retracted. A panel set up by *The BMJ* to consider the matter and led by Iona Heath, former president of the Royal College of General Practitioners, has now concluded that the errors he and others identified, already the subject of corrections, were insufficient, when judged by the criteria of the Committee on Publication Ethics, to justify retraction.[4] Collins, not unexpectedly, disagrees.

The row has set a powerful cadre of experts, led by Collins and including the Cochrane Collaboration, the British Heart Foundation, and the National Institute for Health and Care Excellence (NICE), against a more diverse group of doctors, statisticians, and epidemiologists who question whether the evidence is really so compelling as to justify further extending the availability of statins to lower risk groups.

Among these sceptics is Klim McPherson, a colleague of Collins at Oxford and chair of the UK Health Forum, an alliance of professional and public interest organisations working to reduce the risk of non-communicable diseases. He asked, "Where are the data? It's quite obvious to me that muscular myopathy is much more common than Rory believes and that it's quite disabling," he said. "It's very worrying. NICE has dodged the issue completely by not seeking those data, when it should have done. What is clear is that we don't have adequate data about the side effects, and those data that we do have are misleading."

Others questioning the need to medicalise so many people wrote to the *Times* accusing those responsible for the NICE guideline on statins of having ties to the companies that made them—"a completely unjustified attack on their integrity," retorted Mark Baker of NICE.[5] The signatories to that letter included some heavyweights, such as Richard Thompson, president of the Royal College of Physicians, and Clare Gerada, former chair of the Royal College of General Practitioners.[6]

> "What is clear is that we don't have adequate data about the side effects, and those data that we do have are misleading"
> Klim McPherson, chair, UK Health Forum

Cochrane Collaboration U turn

How did the row ignite, and why did it burn so bright? New readers start here.

At the end of January 2013 the Cochrane Collaboration published an analysis of the use of statins in the primary prevention of cardiovascular disease.[7] Reversing a conclusion it had reached just two years earlier, it said that the evidence now justified the use of statins in people at low risk of cardiovascular disease. The evidence came from the Cholesterol Treatment Trialists (CTT) collaboration, which is led from the Clinical Trials Support Unit at Oxford, co-directed by Collins. The 2013 Cochrane review included as an appendix an exchange with Collins in which he had criticised the 2011 version for not including evidence from a paper the CTT had published in 2010. He called for urgent revision and insisted, successfully, on the correction of the 2011 press release, which he called "dangerously misleading" for saying that statin use in people at low risk might do as much harm as good.

It was in this exchange that Collins first drew a parallel with the MMR scare. Calling for a public retraction by the Cochrane Collaboration of the press release, he wrote, "In public health terms, it is potentially a far more serious misrepresentation than that of the risks of MMR by Wakefield and *The Lancet*." Since readers of the review had not seen the press release, sent only to journalists, the collaboration responded to this demand by sending the same journalists a correction and noting it on its website, in what Collins described as a "misleadingly half-hearted" way. There the matter rested, but a fuse had been lit.

Cochrane did indeed change its mind in the direction Collins wanted, but some experts doubted that the new evidence, including a meta-analysis published by the CTT in 2012, was enough to justify the U turn. In June 2013 John Abramson of Harvard Medical School and colleagues submitted a paper to *The BMJ* challenging the claim that statins reduced all cause mortality and cardiovascular events in people at low risk

Key players in the debate, from left: Rory Collins, Fiona Godlee, Klim McPherson, Iona Heath, and Iain Chalmers

without any increase in adverse events. The CTT's own figures, they said, showed no reduction in all cause mortality. Given this absence of benefit, exposing low risk people to the side effects of statins was unjustified. The paper was published in October 2013.[1]

The claims were challenged in a rapid response to *The BMJ* by the lead author of the Cochrane group, Mark Huffman.[8] While conceding that no strong evidence of a reduction of all cause mortality had been shown, he said that this was because the numbers were small: only 1% of the control group died over four years. He also disagreed with Abramson's interpretation of the evidence.

Personal visits

No blood was shed in this exchange, nor any call for a retraction made. But a few days later Collins visited *The BMJ*'s editor in chief, Fiona Godlee, and raised the temperature. His complaint was that Abramson's statements about the side effects of statins were misleading, claiming that this was worse than the MMR scare and demanding retraction of the Abramson paper and of an Observations article by the cardiologist Aseem Malhotra that had been published in the same issue and included the same claim about the prevalence of side effects.[2] Godlee invited him to write an article putting the points he had made to her on record—an invitation never taken up.

Corrections to the two articles were in due course made—too tardily in the view of the Heath panel—but meanwhile Collins had gone public with his criticisms in the interview in the *Guardian* on 21 March 2014.[3] This generated plenty of follow-up coverage, not all of it entirely accurate. The *Daily Record* said that the papers had been withdrawn, when they hadn't; the *Daily Telegraph* included the same claim in a standfirst over an otherwise accurate article; and in his column in the *Western Mail* Rhodri Morgan, former first minister in the Welsh Assembly, asserted that the papers had included "schoolboy howlers in the statistics, huge miscalculations."

The reality was more modest. Both papers had included the claim that a fifth of people who took statins experienced side effects. This figure came from an observational study by H Zhang and colleagues that actually showed that 18% of statin users had "statin-related clinical events that may be interpreted as adverse reactions by patients or clinicians."[9] The original paper made no claim of causation; the two papers in *The BMJ* did. They were entitled to cite the original work but not to misrepresent it. Most people would not deem this a hanging offence, but Collins's vivid language made it seem worse, and Godlee's initial slip in claiming that the error had been missed by peer reviewers further riled him. In fact, the statistic had been added to Abramson's paper in proof; the reviewers were blameless.

It is plain that trying to close down this particular debate by asserting superior knowledge is unlikely to succeed

"Not a reasonable matter for debate"

In real life, many people who take statins have pains that they attribute to the drugs. Are they deluding themselves by inferring causation where none exists? That is the view of Collins and of the NICE panel—their argument is that in the clinical trials just as many people taking a placebo had joint and muscle pain as in the active drug group. The reason Collins gave for not submitting the response Godlee wanted was, in a letter marked "not for publication": "This is not a reasonable matter for debate, but is instead one of fact: a 'statin-related adverse event' (as studied by Zhang et al) is not necessarily caused by, or a side-effect of, a statin so it is just plain wrong to claim that it is."

It's fair to say, however, that this is a distinction that might be lost on Mr Lowrisk.

Collins's response to the report of the Heath panel was equally dismissive. Conceding that the major error had been corrected, he added that several other serious errors had not yet been withdrawn—despite the finding by the panel that all the other numerical claims made in the Abramson paper were statistically sound.

In real life, many people who take statins have pains that they attribute to the drugs. Are they deluding themselves by inferring causation where none exists?

McPherson said (in an email to Collins) that he found this response "quite shocking." Other Oxford colleagues, including Iain Chalmers, the founder of the Cochrane Collaboration, have tried to broker peace between *The BMJ* and Collins but without success.

Calls have been made for all the patient level data held by the CTT to be released and (by Chalmers) for the statins to be reassessed in a withdrawal trial, where people who complain of side effects are randomly allocated to receive either placebo or to continue the active drug and the outcomes measured. For the moment, however, it is plain that trying to close down this particular debate by asserting superior knowledge is unlikely to succeed.

McPherson says of the situation, "My view is that it's absolutely unsatisfactory as it stands. As more and more people go on to statins, the side effects will become more and more manifest, if they're real, and we'll get to the point where they won't be the drug of choice."

That, of course, would be the reverse of the objective sought by Collins.

Nigel Hawkes freelance journalist, London
nigel.hawkes1@btinternet.com

Competing interests: See bmj.com/about-bmj/freelance-contributors/nigel-hawkes.

Provenance and peer review: Commissioned; not externally peer reviewed.

The independent panel's report and all related materials, including a timeline of events leading up to the report, are at thebmj.com/statins.

Cite this as: *BMJ* 2014;349:g5007

EDITORIAL, p 8

thebmj.com
News: Two doctors die from Ebola and lives of others under threat in west Africa (*BMJ* 2014;349:g4895)
News: Health ministers in west Africa hold crisis talks on Ebola virus (*BMJ* 2014;349:g4478)

Ebola: an opportunity for a clinical trial?

As the largest outbreak of Ebola virus has forced hitherto neglected tropical diseases on to the public agenda, debate is growing over whether affected patients should have the chance to try experimental drugs. **Sophie Arie** reports

YOUSSOUF BAH/AP/PA

A few weeks ago, most people worldwide had probably never heard of Ebola disease. Outbreaks were rare and usually quickly contained. Before the current epidemic, the disease had killed only 1590 people in total, most of them in remote parts of Uganda and what is now the Democratic Republic of Congo, since it was discovered in 1976 (timeline).[1]

Now, Ebola has spread across three densely populated countries in west Africa in less than six months, killing 887 people, and—despite their best efforts to contain it—the World Health Organization and aid agencies have warned that the outbreak is out of control. "If the situation continues to deteriorate, the consequences can be catastrophic in terms of lost lives but also severe socioeconomic disruption and a high risk of spread to other countries," said Margaret Chan, the director general of WHO on 31 July.[2]

Because of fears that air travel could spread the virus almost anywhere, alarm bells are suddenly ringing worldwide. Borders and airports in the affected countries have been closed, and in the West headlines about a pandemic threat have appeared, with calls for a vaccine and a cure.

A possible turning point?

Will this extraordinary Ebola epidemic prove to be a turning point in terms of the world's attitude towards this—and other—deadly but hitherto neglected tropical diseases? "There's an opportunity here. Whether or not it will be seized remains to be seen," Peter Walsh, an Ebola specialist at Cambridge University, told *The BMJ*. "Several experimental vaccines have been highly successful in animals. They should be used now to save lives and to carry out a clinical trial."

"The odds are that these vaccines are safe," says Walsh, who has worked on one experimental vaccine. "When probable benefits outweigh probable risks, there's obviously a net benefit." Yet people fighting the outbreak on the ground, where tensions are high amid fear and mistrust of foreign doctors, say it would be unwise to start experimenting with new drugs now.

In an atmosphere of growing panic, the idea of Western doctors injecting African people with experimental drugs seems potentially disastrous

Ebola haemorrhagic fever is a horrific disease that first involves flu-like symptoms, diarrhoea, and vomiting but can rapidly cause internal and external bleeding and organ failure. It is only transmitted through contact with bodily fluids during the final stages of the disease, however, which means that in the past containment has always been possible through simple techniques, involving isolation of infected people, contact tracing, and good hygiene.

TIMELINE: EBOLA

1976 >>>

Ebola first appears in two simultaneous outbreaks, in Nzara, Sudan, and in Yambuku, Democratic Republic of Congo (called Zaire at the time). The latter was in a village situated near the Ebola River, from which the disease takes its name. It is thought to be transmitted to humans from fruit bats

1976–2012 >>>

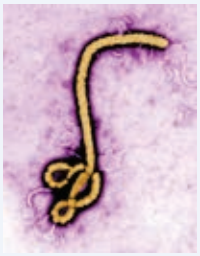
24 outbreaks of Ebola are reported—five in Uganda, six in DR Congo, four in Congo-Brazzaville, three in Sudan, four in Gabon, one in Ivory Coast, and one in South Africa. The largest was in Uganda in 2000 when 425 people died. Little funding is available for research, and the basic facts about the origin of the disease and its behaviour are not discovered.

2001 >>>

The US and other countries begin investing in research towards developing treatments and vaccines for Ebola and other so called neglected tropical diseases as part of the post-9/11 bioterrorism campaign

2010-12 >>>

Several studies for possible treatments and vaccines show promising results in primates and mice



Ebola has spread across three densely populated countries in west Africa in less than six months, killing more than 887 people, and aid agencies have warned that the outbreak is out of control

WHO, which is leading the effort to support the affected countries, has acknowledged that because of the unique conditions in west Africa the virus is still "moving faster than we are." The region has never experienced Ebola before, so the virus was able to circulate for more than three months before it was identified.[3] This is a densely populated region, where the infrastructure is better than elsewhere in Africa and the population is highly mobile. But Guinea, Liberia, and Sierra Leone are among the poorest countries in the world[4]; health services are very basic (some places have no running water) and the least equipped to cope. Fear, lack of understanding of the disease, and burial traditions mean that the public have not avoided contact with people who have been infected, and many people have been too afraid to seek medical help. Some even believe that doctors are spreading the disease.[5]

Recognising the scale of the challenge, WHO has just announced that it will spend $100m (£59m; €75m) on deploying many more experts and vast quantities of equipment. The World Bank has also pledged $200m. International aid agencies MSF and the International Committee of the Red Cross both expressed hope in late July that with far greater resources the disease can be contained by the end of the year. No one is willing to estimate how many people may have died by then. Although there are signs that the virus has peaked in Guinea, where the outbreak started in March, a second case of Ebola has now been reported in Nigeria.

Can experimental drugs be used?

Although WHO and international aid agencies would like to be able to offer both vaccines and therapeutic treatments to the affected population, they insist that for ethical and practical reasons, the drugs must be tested on humans first. "As doctors, trying an untested drug on patients is a very difficult choice since our first priority is to do no harm and we would not be sure that the experimental treatment would not do more harm than good," Bart Janssens, MSF's director of operations, told *The BMJ*.

In an atmosphere of growing panic—with schools closed in affected areas, government workers sent on compulsory leave for a month, and people fleeing—the idea of Western doctors injecting African people with experimental drugs seems potentially disastrous. If the drugs worked, there could be a sudden clamour for them to be given to millions of people when only limited numbers of samples are currently available. If the drugs failed, there could be a huge backlash against the doctors who administered them.

"The experimental vaccines and treatments that are most promising in animal studies work best when given in the earliest stages of infection," said Heinz Feldmann, an Ebola expert who heads the laboratory of virology at the US National Institute of Allergy and Infectious Diseases' Rocky Mountain Laboratories in Hamilton, Montana. "In west Africa right now, people are turning to doctors only when the symptoms are already very advanced. At that stage, no experimental drug can save them."

The governments battling the outbreak have not called for experimental drugs to be made available, Feldmann points out, and securing informed consent for trials in the population would be a huge problem. The time and cost of manufacturing sufficient volumes of a new drug for human use are another consideration. Until now, that investment has simply not made economic sense for either drug companies or governments, because the disease affects only relatively small numbers of people in poor countries.

The US government has invested more than any other country in researching neglected tropical diseases since the 9/11 terrorist attacks raised fears about possible bioterror attacks.[6] That investment had led to several experimental treatments and vaccines having shown potential during laboratory testing (box).

2014 >>>

March

Ebola virus outbreak confirmed in Guinea. Subsequent tracing shows that the disease had first struck in December 2013. It is thought to have been carried to Guinea from Gabon

Ebola reported in Liberia at the end of March

May

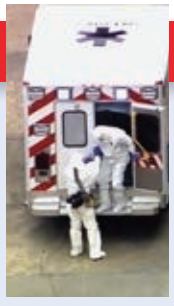
Ebola reported in Sierra Leone

23 June: Médecins Sans Frontières (MSF) declares that the outbreak is "out of control," with more than 60 hotspots where the cases have been reported. 337 people were confirmed dead at that stage

20 July: A man arrives at Nigeria's Lagos airport with Ebola symptoms, triggering concern worldwide that the disease could spread internationally by plane

25 July: Sierra Leone's top Ebola doctor, Sheik Umar Khan, succumbs to the disease. More than 100 medical workers are known to be among the dead

31 July: WHO announces $100m to upscale the effort to contain the disease, and secretary general Margaret Chan warns of "catastrophic numbers of dead" if the disease is not brought under control. WHO staff and aid agencies on the ground say there are signs in some areas that numbers of new infections are beginning to fall. In total, 729 people are confirmed dead. The same day, the US announces the bringing forward of a clinical trial of a possible vaccine



1 August: Two infected US citizens are flown home from Liberia where they had been working with Ebola patients. One of them was reportedly given an unnamed experimental serum to treat the disease. Another infected colleague reportedly took a serum of antibodies taken from a survivor. At the time of publication, their condition was not known

Experimental treatments and vaccines

- Tekmira pharmaceuticals, a British Columbia based company, has developed a treatment based on so called RNA interference, which works to block DNA making proteins and stop the virus replicating. The drug was in phase I trials, but the US Food and Drug Administration (FDA) halted them in 2012 to investigate the process, which would involve a "heavy dosing regimen."
- A North Carolina company, BioCryst Pharmaceuticals, has used the same technique to develop a drug, with a working name of BCX4430, which has proven effective in animal studies in preventing deaths from the Marburg virus, which is similar to Ebola.
- Another promising approach, based on creating a cocktail of antibodies taken from survivors of the disease, has also proven highly successful in animal trials. Results are expected to be published in the coming months.
- The most promising vaccine is made from a microbe called vesicular stomatitis virus (VSV).

SUNDAY ALAMBA/AP/PA

Nigerian officials wait to screen passengers at Lagos Airport

Clinical trials for safety are expensive, however, and efficacy trials can be conducted only during an outbreak. The FDA halted two safety trials on experimental Ebola drugs in recent years, one as a result of funding problems; only in 2012, experts were saying that developing these drugs might never be possible.[7]

So will the scale of the current outbreak change that? "It would be great if this could be a wake-up call for this issue," says Peter Hotez, director of the Sabin Vaccine Institute in Washington. "But I don't know if this [outbreak] will be enough of a game changer because it's not big enough. Malaria kills as many people each day as this outbreak has killed so far. We must try to keep things in perspective."

The only positive development to come from the epidemic is that it has attracted long needed attention from drug makers

Anthony Fauci, director of America's National Institute of Allergy and Infectious Diseases, has just announced that a phase I clinical trial of a promising Ebola vaccine will be brought forward to start this September. Results should be ready by January; if they show that the vaccine is safe for healthy people and effective in terms of prompting the development of antibodies, the vaccine could be manufactured for human use later next year, Fauci said. It could then be given to health workers who are both at high risk of infection and so called "superspreaders" of the disease because of the physical contact they have with patients. Because of their professional expertise, they would also be best placed to give informed consent to participate in a trial. The only positive development to come from the epidemic is that it has attracted long needed attention from drug makers, Fauci said.

Under FDA regulations, in an emergency the "two animal rule" can be applied so that as long as a drug has shown efficacy in two different animals and has proven not to have serious side effects in healthy humans, it can be made available on compassionate grounds.[8] But even the US's efforts to fast track the approval of experimental drugs in this way will prove too late for the victims of the current outbreak.

Walsh says that if $10-20m had been found to fast track experimental drugs in March—only a fraction of what is now being spent to contain this outbreak—a vaccine and a treatment would be available by now, the outbreak would be under control, and drugs could be stockpiled for any future outbreaks or bioterrorist attacks.

"Plague vaccines were developed by testing experimental treatments on victims," he says. Because of concerns about the ethics of experimenting on African patients, however, nobody is brave enough to start testing drugs that have not gone through the rigorous Western approval process. Whereas Westerners might immediately consent to trying an experimental drug faced with the 56% chance of death in the current epidemic, in Africa there is a deep seated mistrust around drug trials conducted by foreign organisations."

Walsh believes, however, that if small numbers of medical professionals were seen to be cured or immunised against the disease by experimental drugs, the affected population and their governments would rapidly be won round. "There has to be a change in the policy elite about what is the right thing to do," he says. "It's in everybody's interests."

Who should take responsibility?

Walsh suggests that the UN and international organisations are hamstrung by bureaucracy and an aversion to risk taking. Drug companies are not willing to take on the legal responsibility. "What's needed is insurgents from outside to come and change the culture."

Jeremy Farrar, director of the Wellcome Trust and a professor of tropical medicine, might prove to be just that. He has called for a major rethink in the current approach. "Not a single individual has been offered anything beyond tepid sponging and 'we'll bury you nicely,'" he said in early July. "It's just unacceptable."

Despite recent efforts to improve the way the world works together against potential global health threats,[9] resistance to testing new treatments during outbreaks, wherever they are, has to be overcome, Farrar says. "We need to work with at-risk communities and national governments to discuss potential new treatments and how they might work within ethical, logistical, and assessment frameworks, and we need them to be ready to go within days," he argues.[10] "We also have to work out how to ethically, and practically, undertake the essential clinical research in an emergency that is critical to save lives and reduce disease transmission."

The Wellcome Trust has proposed that it could potentially fund and organise such trials, in the hope that experimental drugs will be stockpiled so that next time Ebola—or another neglected tropical disease—strikes, the victims might have a chance to try them.

Sophie Arie freelance journalist, London
sarie@bmj.com

Competing interests: None declared.

Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2014;349:g4997

LAST WORDS, p 37