



Knowledge gaps about Tamiflu and Relenza for pandemic flu are blamed on research failure

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A failure to carry out research during the 2009 flu pandemic has left the world unprepared for another one, with huge gaps in the knowledge base that should by now have been filled, says a report from the Academy of Medical Sciences and the Wellcome Trust.¹

Research into infectious diseases is “woeful,” said Jeremy Farrar, director of the trust, at a briefing to introduce the report at the Science Media Centre in London. No vaccines were available to prevent severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS), he said, and it had taken six to nine months to set up trials for an Ebola vaccine. Furthermore, the numbers involved in trials during the 2009 H1N1 flu pandemic had been “close to zero.”

As a result, it is not known how well antiviral drugs such as oseltamivir (Tamiflu) and zanamivir (Relenza) work against pandemic strains of flu. The evidence from seasonal flu, summarised in the report, is that the drugs have a modest effect of shortening the duration of symptoms by 14-18 hours in patients treated in the community, a benefit that is unlikely to outweigh the risks of side effects. The same is true in over 65s and in patients with comorbidities.

Among patients whose condition is serious enough to justify hospital admission, antivirals do reduce mortality, especially if taken within 48 hours of the first onset of symptoms. But the evidence from observational studies of the 2009 pandemic involves a lot of missing or unobtainable data that could have been remedied by a randomised controlled trial.

For prophylaxis, the evidence base is similarly incomplete. In the community, three cases might be prevented in every 100 people treated, and, within households, 13 cases prevented might be prevented in every 100 treatments, said Chris Butler, of the University of Oxford. In care homes, evidence was particularly lacking, so judgment had to be made on a case by case basis, depending on the severity of the outbreak, he added.

These conclusions do not differ significantly from those reached previously by others. So, was the £424m (€575m; \$650m) spent by the UK government on stockpiling Tamiflu in 2009, plus another £136m on Relenza, money wasted? Farrar said, “Politics is a complex art, and I believe it was right to stockpile. Imagine the opposite scenario, with an outbreak of bird flu with a 5%

mortality, if the government had not done what it did.” This, he said, was a personal view, and this question was not tackled in the report.

The strongest theme in the report was the need to seize the opportunity of seasonal and pandemic outbreaks to conduct randomised controlled trials for both. The problem, said Butler, was the time that this took, as researchers had to “walk through treacle” to gain ethical consent and set up such a trial.

Progress has been made, however, and Butler is coordinator of a trial funded by the European Union that will recruit patients this winter. The antiviral for flu-like illness study (ALIC4E) seeks to recruit 4500 patients in 20 countries during three winter seasons, randomising them to normal care or to normal care plus Tamiflu. Results will be analysed as they are generated, rather than after the trial is over, so that treatment can be tailored during the course of the epidemic.

In principle, treatments could be changed or the trial continued if a pandemic strain appeared, although making changes is “extremely cumbersome,” Butler admitted. Neither he nor Farrar had any ethical doubts about the trial, arguing that, given the present state of knowledge, it would be unethical not to conduct it. “We’ve been talking about this for 10 years,” said Farrar. “Now everyone’s persuaded. Getting it set up is a major advance.” Trials are also needed in hospitalised patients and in prophylaxis, the report said.

Carl Heneghan, professor of evidence based medicine at Oxford, who was not a member of the report committee, said, “The implications of this report should not be underestimated: the misinterpretation of the evidence to date has wasted scarce resources and led to widespread confusion.

“Use of antivirals in a pandemic would not be based on the best available evidence, but principally on poor quality evidence and opinion. This is primarily due to the failure to undertake trials in the last outbreak.”

1 Academy of Medical Sciences, Wellcome Trust. Use of neuraminidase inhibitors in influenza. Oct 2015. www.acmedsci.ac.uk/publications/.

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