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Influenzae

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The Cochrane Collaboration



The Cochrane Collaboration is a not-for-profit international network of researchers, practitioners and consumers who prepare and update systematic reviews of the effects of healthcare interventions (drugs, vaccines, devices, procedures, service delivery, training, quality control mechanisms etc). Cochrane reviews seek to bring together all of the research on a topic, to minimise bias and to provide independent, reliable information to help decision makers. There are now more than 4000 full Cochrane reviews. The Collaboration has a structure including thirteen Cochrane Centres and just over 50 Cochrane Review Groups spread around the world (1). These Groups provide the editorial oversight for the reviews. The work on the reviews is done by a network of thousands of individuals. I am one of them. Each Centre and Group is self financing, with the bulk of the funding coming through government agencies. Most of my influenza Cochrane work was funded by the Italian MoH and the Piemonte Region, the UK's National Institute for Health Research (NIHR) and the Australian National Health and

Medical Research Council. Several studies have shown the high quality of Cochrane reviews (2-5).

Objective

In this presentation, I will summarise the evidence on 4 main points which in my view are key to recent events, give you my interpretation and leave time for questions.

Influenza and influenza-like illness are not the same thing

We start with what we see sometimes several times a year: influenza-like illness (“the flu”). The WHO defines influenza-like illness as “an acute respiratory infection with sudden onset characterised by fever $>38^{\circ}\text{C}$ and at least one of the following: headache, malaise, rigors and sweating, asthenia and at least one respiratory symptom such as rhinitis and pharyngitis”. We are all familiar with this illness but what most people are not told is that the influenza viruses only account for a minority (7-15%) of these episodes. Instead, the world seems to believe that all flu is influenza and ignores the role of some 200 other agents. This is possible because physicians and patients cannot tell influenza apart from (for example) “flu” episodes caused by rhinovirus 16 or metapneumovirus (other common agents of flu), without special tests. The signs and symptoms look and feel all the same.

The clinical entity presenting is that of a syndrome commonly known as influenza-like illness or ILI for short. The term **syndrome** refers to the association of several clinically recognizable features, signs (observed by a physician, e.g. cough), symptoms (reported by the patient, e.g. fatigue), phenomena or characteristics that often occur together, so that the presence of one feature alerts the physician to the presence of the others (6).

A syndrome has many causes as is the case with influenza-like illness (“the flu”)

Understanding how many influenza-like illness (“flu”) episodes are truly influenza (i.e. are caused by influenza viruses A and B) is vital, if we are to stop what governments,

experts and the public continue doing: confusing the two. This confusion magnifies the threat of influenza.

The starting point is that few (if any) national and international surveillance systems make the distinction between influenza and influenza-like illness either because they do not believe the question is important, because the “system“ is not geared up for it or for other still unclear reasons. The effect however is that people reporting the impact of ILI, usually call it influenza. Here lies the second reason: the confusion in terminology between “flu”, “influenza-like illness - ILI”, “acute respiratory infection - ARI”, “influenza”, “common cold”, “upper respiratory tract infection - URTI” belies the lack of clarity as to the epidemiology of ILI and influenza. This confusion comes from history, familiarity and ignorance. The equation “flu=influenza” is now so ingrained in the popular and sometimes professional mind that governments and public fall pray to its greatest consequence: that of overestimating the impact of influenza, which is usually a benign self limiting infection.

Another consequence is the idea that influenza-like illness (“flu”) and its ravages can be prevented or minimised with influenza vaccines. Cochrane reviews show that vaccines could only affect **at the most** (i. e. if they had 100% efficacy) some 7-15% of the annual flu burden, since this is the proportion of people with the flu who truly have influenza. This “specificity” of approach (go for influenza, disregard all other causes of the flu) is probably based on what I call availability creep (let’s concentrate on influenza because that’s the one we have specifics for). But, if you think about it, it is a wonderful utopian policy against a syndrome as unspecific as this (just think of the role that other viruses play). In my opinion, the lack of logic in this thinking is stunning (7).

Effectively what we are saying is we aim to control a major health problem, influenza-like illness (“the flu”), with a series of preventive interventions which can in the best case scenario prevent only 15% of that problem, while making people believe we can deal with the lot.

Available policy documents recommend preventing influenza by vaccinating different segments of the population before the “season”. In our hemisphere this usually means

the period of maximum circulation and transmission of influenza viruses. This however is also the period of circulation of several other agents. The autumn-winter time is the time when (for example) we would expect Rhinoviruses, Parainfluenza Viruses and Respiratory Syncytial Viruses to be circulating. These cannot be attacked by the influenza vaccine.

In other words vaccination programmes are directed against what surveillance systems worldwide call “influenza” but in reality are influenza-like illness/flu. Surveillance systems cannot distinguish the two and provide reliable estimates of impact. This point is the key to understanding what comes next. The false equation “influenza-like illness/flu =influenza” has misled some of the research on the effects of influenza vaccines and (most of all) the interpretation of such evidence.

Influenza surveillance programmes in different places appear to report on the presence and degree of threat of influenza but what they are really looking at are influenza-like illness/flu. I can illustrate this by looking at perhaps the biggest and most complex system of them all: the USA’s. The data I will show you now were gathered by Peter Doshi, a graduate student on his way to a Doctorate at MIT to whom I am grateful for permission to use his data.

Peter tried to find out if the US system really was about influenza-like illness/flu or influenza. The question he asked was: what percentage of influenza-like illness/flu was influenza?

Peter got 43 out of 51 possible oral or electronic interviews. The slide shows some of the most colourful answers from the State Epidemiologists or Influenza Coordinators. They all say the same thing but in different ways: “we do not know”.

Most understood the question, but still could not provide an answer because their surveillance systems were not focused on this question. There is an emphasis on the influenza agent only (any biological specimen which is not positive for influenza is thrown away) and the specimens reported thus represent an unreliable and biased estimate of the truth. So we have no idea how much ILI/flu there is and as consequence

we cannot say for certain how much influenza is circulating as influenza is an unknown proportion of an unknown whole (influenza-like illness/flu).

In conclusion the currently available evidence does not allow us to know in a reliable way how many cases of influenza there are, nor its impact in terms of death and disability with any degree of certainty. However the confusion between influenza and influenza-like illness (“the flu”) has led to an obsession with a single agent (the influenza virus) which is not based on any sound evidence and, as I hope you now realize, is potentially dangerous and misleading (because even a perfect vaccine can not work against influenza-like illness/flu as a whole).

Seasonal and pandemic influenza

One of the consequences of our lack of knowledge of the true impact of influenza (I am disregarding the much vaunted yearly models which are little more than guesswork when based on biased primary data) is that if we cannot describe the ordinary (i.e. the seasonal) in any satisfactory way, we certainly cannot describe the extraordinary (i.e. pandemic).

This may be one of the reasons why WHO has changed the pandemic definition so many times since early May 2009.

The definition before May 4 2009 (which has since disappeared from the WHO website and is no longer available in the cache of old web pages) was as follows (with emphasis by me):

“An influenza pandemic occurs when a new influenza virus appears against which the human population has no immunity, resulting in epidemics worldwide with **enormous numbers of deaths and illness**. With the increase in global transport, as well as urbanization and overcrowded conditions, epidemics due the new influenza virus are likely to quickly take hold around the world”

But this was changed around that time, with the same web page becoming the following:

“A disease epidemic occurs when there are more cases of that disease than normal. A pandemic is a worldwide epidemic of a disease. An influenza pandemic may occur when a new influenza virus appears against which the human population has no immunity..... Pandemics can be either mild or severe in the illness and death they cause, and the severity of a pandemic can change over the course of that pandemic”.

WHO spokeswoman Natalie Boudou justified the change by saying that the “old” definition was in “error” and had been taken out of WHO web site. "It was a mistake, and we apologize for the confusion," she said. "(That definition) was put up a while ago and paints a rather bleak picture and could be very scary." The correct definition is that "pandemic" indicates outbreaks in at least two of the regions into which WHO divides the world, but has nothing to do with the severity of the illnesses or the number of deaths." (8)

We now had a third definition in which viral spread is present in at least two WHO regions. However Dr Gregory Hartl, a spokesperson for WHO added a further dimension to our evolving understanding of a pandemic on 9 February 2010 when he was interviewed by the Italian Swiss TV news programme “Falò”. He said: “large organizations such as ours have enormous websites. These contain old pages dating back five or six years. We wrote that definition [i.e. the one pre-dating 4 May 2009] with avian flu in mind, but it is still on our website – we like transparency we do not want to hide anything.”

Swiss TV could not find the cached web page, but Dr Hartl introduces the novel concept of a virus-specific (i.e. A/H5 N1) pandemic definition. Neither this interpretation (nor its “regional” variant of Ms Boudou) are however comforted by looking at the relevant parts of important WHO documents predating May 4 2009.

Here are a few quotes:

“most users of this guide will be broadly familiar with the nature of the threat posed by influenza pandemic. Such an event occurs with the appearance of a new subtype of influenza ‘A’ virus, against which most of us have no immunity, resulting in a global impact with high numbers of cases and deaths. Increases in both local and global transportation, overcrowding in urban settings and marginal sanitary conditions in parts of the world will contribute to a very rapid spread of a pandemic virus. Such a pandemic will be considered a global emergency, requiring management of consequences across multiple jurisdictions and sectors of society”(9).

“The potential for an influenza pandemic with **enormous mortality and morbidity** poses an increasing threat to our world of easy international travel, concentrated population centers and large numbers of people not receiving adequate health care” (10).

“Influenza pandemics are sudden and unpredictable yet inevitable events. They have caused several global health emergencies during the last century. The first and most severe of these is estimated to have resulted in more than 40-50 million deaths worldwide (Ref). Experts anticipate that the next pandemic, whenever it happens, will be associated with a high death toll and a high degree of illness requiring hospitalization, thus producing a considerable strain on health care resources. Pandemics are global by their very nature, and few countries are likely to be spared. In developing countries, where health care resources are already strained and the general population is frequently weakened by poor health and nutritional status, the impact is likely to be greatest (Annex 1)” (11).

“A pandemic is likely when large sections of the population around the world lack immunity to the new virus (i.e., have no or little antibody to the HA of the novel virus), and it is readily transmissible from person to person, causing serious disease. A

pandemic is considered imminent when the new virus spreads rapidly beyond the community in which it was first identified” (11).

“Of the three pandemics of the previous century, those beginning in 1957 and 1968 caused large numbers of cases and a combined mortality estimated at more than three million deaths, mostly in the very young, the elderly and people with underlying chronic conditions. In stark contrast, the 1918 pandemic probably caused more than 40 million deaths, mainly in persons aged 15 to 35 years. The reasons for this exceptional lethality are not fully understood” (12).

“An influenza pandemic occurs with the appearance of a new influenza virus against which none of the population has any immunity. This results in several simultaneous epidemics worldwide with enormous numbers of cases and deaths. With the increase in global transport and communications, as well as urbanization and overcrowded conditions, epidemics resulting from a new influenza virus are likely to be established quickly around the world” (13).

“An influenza pandemic (or global epidemic) occurs when a new influenza virus subtype appears, against which no one is immune. This may result in several simultaneous epidemics worldwide with high numbers of cases and deaths. With the increase in global transport and urbanization, epidemics caused by the new influenza virus are likely to occur rapidly around the world” (14).

So I think we can safely conclude that no one has now any firm idea of how to define an influenza pandemic.

The role of experts and the media

Much has been said about the role of experts in advising policy makers on both seasonal and pandemic influenza. We know that some of them have been parsimonious with declaring their interests and their role as members of lobbying organizations which are financed by industry and some did not think it important to disclose pretty hefty industry funding of their institutions. We know that transparency is probably not taken very seriously by WHO. However, few people realize that even experts with no ties to industry or government civil servants have career motivations, especially if they make policy and evaluate its effects. I'll leave the description of how this works to Professor Philip Alcabes in his modern classic Dread:

“We are supposed to be prepared for a pandemic of some kind of influenza because the flu watchers, the people who make a living out of studying the virus and who need to attract continued grant funding to keep studying it, must persuade the funding agencies of the urgency of fighting a coming plague”(15).

Before you start wondering how I can myself escape this kind of criticisms I would like to inform readers that 2 months before the hearing I circulated a note of activities and interests in which I disclose all that I can think are relevant to this debate. The note was sent to the Secretariat and can be viewed by any member of the Commission. In addition I would like to remind you of what I have written and stated to the media countless times since 2004: beware of catastrophic predictions, stick to the scientific evidence: all the evidence, not just what supports your theories (16).

Few realize that most experts (or KOLs - key opinion leaders - as they are known by communication agencies) do not just appear like daisies in a field, they are “made” over decades after having been recruited by specific image or communications agencies (such as Wolters Kluwer

http://pharma.wkhealth.com/pt/re/ps/page.htm;jsessionid=LjqWgdqBMfbhPCVyBY3IVM PWjPGBTvVJKqcjQj6kgQXTy1L1v1!!276643337!181195629!8091!-1?short_name=p1_kold&menu_type=pc accessed 18 March 2010)

or

Sacoor Ltd (<http://www.sacoormedicalgroup.com/kol.html> accessed 18 March 2010)

KOLs are specifically recruited to “spin” science and help sell products and ideas. They are not all the same, as their worth is measured by their ability to influence.

(<http://pharmexec.findpharma.com/pharmexec/article/articleDetail.jsp?id=197784>

accessed 18 March 2010)

I conclude that the results of the expert system (in which selection is on the basis of fame or sponsorship, with transparency being the exception) are plain for all to see: catastrophic predictions that have failed to materialize, poor science, a thriving pandemic industry and the reputation of public health structures in tatters.

Then we have the media (whose role is plain for all to see) and the scientific media, the scientific journalists, who also had a major role to play, as I shall demonstrate shortly. The media, like everyone else, are cashing in the whole circus.

The Cochrane Collaboration has been doing systematic reviews of the effects of vaccines and antiviral drugs against influenza since the late 1990s. Vaccines and antivirals are useless against the majority of cases of influenza-like illness/flu, as one would expect (17-25). Their effects could only be against those cases caused by the influenza virus itself. No one disagrees on this point. And, in fact, vaccines and antivirals have a weak or non-existent evidence base against influenza. The quality of influenza vaccines studies is so bad that our systematic review of 274 vaccines studies which had published between 1948 and 2007 found major discrepancies between data presented, conclusions and the recommendations made by the authors of these studies. There was an inverse relationship between methodological quality and direction of study conclusions. Conclusions favourable to the use of influenza vaccines were associated with lower quality studies, with the authors making claims and drawing conclusions

unsupported by the data they presented. In addition, industry funded studies were more likely to have favourable conclusions, be published in significantly higher impact factor journals (ie the more prestigious journals) and have higher citation rates than non-industry funded studies. This difference is not explained by either the size or the methodological quality of the studies (26). So, we have little reliable evidence on the effects of influenza vaccines. What we do have is evidence of widespread manipulation of conclusions and spurious notoriety of the studies.

In one of our reviews, we compared mean Journal Impact Factor and Citation rates of all the comparative influenza vaccines studies we had found, looking also at study size and methodological quality. A higher mean journal impact factor and higher citation rates were associated with complete or partial industry funding. Industry funded research tends to target higher impact factor journals (is it not what we all do?), but there appears to be something to do with their sponsorship which makes them more attractive to higher JIF journals and more likely to be cited (26). Does this finding provide another piece in this complex puzzle of interdependence between the scientific media, research and the influenza industry?

Vaccines and antivirals have a weak or non-existent scientific evidence base

After reviewing more than 40 clinical trials, it is clear that the performance of the vaccines in healthy adults is nothing to get excited about. On average, perhaps 1 adult out of a 100 vaccinated will get influenza symptoms compared to 2 out of 100 in the unvaccinated group. To put it another way we need to vaccinate 100 healthy adults to prevent one set of symptoms. However, our Cochrane review found no credible evidence that there is an effect against complications such as pneumonia or death (22).

Cochrane reviews also allow us to investigate the effects of drugs such as the antivirals, and to avoid emphasis on the most exciting results from a subset of the research. Our Cochrane reviews found that antiviral drugs are effective against symptoms, but they are toxic, some are expensive and may not prevent complications (19, 27). In other words, the publicly available evidence suggests that drugs like aspirin may be just as

good, and less dangerous, than the drugs on which billions of Euros have been spent to create stockpiles. This is, of course, not the way they have usually been portrayed in the media. In addition it seems that no one wants to test the performance of antivirals against anti pyretic and anti inflammatory drugs and physical interventions (such as masks or handwashing) to have a definitive answer.

Public health interventions such as hygiene measures and barriers have a much better evidence base than vaccines (28). They are also cheaper and socially acceptable, as well as being life savers in poor countries, yet they are almost ignored. For example, in the most recent 62-page guidance document on planning for pandemic influenza from the World Health Organization, handwashing and masks were mentioned only twice and gloves and gowns once each, but vaccines and antivirals appeared 24 and 18 times, respectively (29). To give some idea of how they compare with influenza vaccines as a public health measure 6 studies carried out in the Far East during the 2003 SARS epidemic shows that just 3-4 people have to wash hands, and wear masks to prevent one case of SARS (28).

Conclusions

In conclusion, I cannot predict the future but if it repeats the past it will be full of continuous alarms and possible declarations of pandemics. If the complex interplay of poor science, KOLs, media business, pharma business, pandemic business and unaccountable decision-making is not interrupted, we will have many more similar episodes. Scientific evidence, systematically and independently assembled and weighted by its quality, needs to be centre-stage and not simply a “pretty maiden” whose services are called upon on demand.

Bibliography

1. www.cochrane.org
2. Moher D, Tetzlaff J, Tricco AC, Sampson M, Altman DG. Epidemiology and Reporting Characteristics of Systematic Reviews. PLoS Medicine 2007; 4(3): e78.

3. Wen J, Ren Y, Wang L, Li Y, Liu Y, Zhou M, Liu P, Ye L, Li Y, Tian W. The reporting quality of meta-analyses improves: a random sampling study. *Journal of Clinical Epidemiology* 2008; 61: 770-775
4. Moseley AM, Elkins MR, Herbert RD, Maher CG, Sherrington C. Cochrane reviews used more rigorous methods than non-Cochrane reviews: survey of systematic reviews in physiotherapy. *Journal of Clinical Epidemiology* 2009; 62(10): 1021-1030
5. Lundh A, Knijnenburg SL, Jørgensen AW, van Dalen EC, Kremer LCM. Quality of systematic reviews in pediatric oncology: a systematic review. *Cancer Treatment Reviews* 2009; 35: 645-652
6. Last JM, Spasoff RA, Susan S (editors). *A Dictionary of epidemiology*, Fourth Edition - ISBN 0195141687, 2001 Oxford University Press, New York.
7. Jefferson, T. Guest Editorial: Mistaken identity: seasonal influenza versus influenza-like illness. *BMJ Clinical Evidence* 5 October, 2009.
8. Elizabeth Cohen, "When a pandemic isn't a pandemic," CNN.com, May 4, 2009, <http://www.cnn.com/2009/HEALTH/05/04/swine.flu.pandemic/index.html?iref=allsearch> (accessed 18 March 2010)
9. World Health Organization. WHO Western Pacific Region: Exercise Development Guide for Validating Influenza Pandemic Preparedness Plans. www.wpro.who.int/.../WHO+Influenza+Pandemic+Preparedness+Checklist.pdf (accessed 2 Feb 2010) (pdf page 1).
10. World Health Organization. *Avian Influenza: Responding to the Pandemic Threat* http://www.searo.who.int/LinkFiles/Avian_Flu_influenza_vaccine_development.pdf (accessed 2 Feb 2010) (pdf page 6).

11. World Health Organization. Guidelines on the Use of Vaccines and Antivirals during Influenza Pandemics. Geneva: WHO 2004 WHO/CDS/CSR/RMD/2004.8 (pdf pages 5 and 15) (pdf page 1)
12. World Health Organization. Strengthening pandemic influenza preparedness and response. Report by the Secretariat 7 april 2005. Geneva: WHO A58/13 Pdf page 3.
13. World Health Organization. Informal consultation on influenza pandemic preparedness in countries with limited resources Kuala Lumpur, Malaysia 23–25 June 2004. Geneva: WHO 2004. WHO/CDS/CSR/GIP/2004.1. Pdf page 5
14. World Health Organization. WHO checklist for influenza pandemic preparedness planning Geneva: WHO 2005 WHO/CDS/CSR/GIP/2005.4. Pdf page 6
15. Philip Alcabes. Dread: How Fear and Fantasy Have Fueled Epidemics from the Black Death to the Avian Flu. Public Affairs. ISBN: 978-1586486181.
16. Jefferson T. What are we to do about influenza? (Editorial). *BMJ* 2004; 329: 633-4.
17. Jefferson T, Di Pietrantonj C, Al-Ansary LA, Ferroni E, Thorning S, Thomas RE. Vaccines for preventing influenza in the elderly. *Cochrane Database of Systematic Reviews* 2010, Issue 2. Art. No.: CD004876. DOI: 10.1002/14651858.CD004876.pub3.
18. Thomas RE, Jefferson T, Lasserson TJ. Influenza vaccination for healthcare workers who work with the elderly. *Cochrane Database of Systematic Reviews* 2010, Issue 2. Art. No.: CD005187. DOI: 10.1002/14651858.CD005187.pub3.
19. Tom Jefferson, Mark Jones, Peter Doshi, and Chris Del Mar. Neuraminidase inhibitors for preventing and treating influenza in healthy adults: systematic review and meta-analysis. *BMJ*. 2009; 339(dec07_2): p. b5106.
http://www.bmj.com/cgi/content/abstract/339/dec07_2/b5106?ct=ct

20. T Jefferson, A Rivetti, A Harnden, C Di Pietrantonj, and V Demicheli. Vaccines for preventing influenza in healthy children. *Cochrane Database Syst Rev* 1 Jan 2008: p. CD004879
21. C Cates, T Jefferson, and B Rowe. Vaccines for preventing influenza in people with asthma. *Cochrane Database Syst Rev* 1 Jan 2008: p. CD000364.
<http://highwire.stanford.edu/cgi/medline/pmid;18425863>
22. TO Jefferson, D Rivetti, C Di Pietrantonj, A Rivetti, V Demicheli. Vaccines for preventing influenza in healthy adults. *Cochrane Database of Systematic Reviews* 2007, Issue 2. Art. No.: CD001269. DOI: 10.1002/14651858.CD001269.pub3.
23. Jefferson T, Rivetti D, Rivetti A, Rudin M, Di Pietrantonj C, Demicheli V. Efficacy and effectiveness of influenza vaccines in the elderly: systematic review. *Lancet* 2005 ; 366:1165 -1174.
24. Jefferson T, Smith S, Demicheli V, Harnden A, Rivetti A, Di Pietrantonj C. Assessment of the efficacy and effectiveness of influenza vaccines in healthy children: systematic review. *Lancet* 2005; 365:773-80.
25. T Jefferson, C Di Pietrantonj, M G Debalini, A Rivetti, and V Demicheli. Inactivated influenza vaccines: Methods, policies, and politics. *J Clin Epidemiol* 2008; 1-10. <http://highwire.stanford.edu/cgi/medline/pmid;19124222>
doi: 10.1016/j.jclinepi.2008.07.001.
26. T Jefferson, C Di Pietrantonj, MG Debalini, A Rivetti, V Demicheli. Study quality, concordance, take home message, funding and impact. Their relationship in influenza vaccines studies. *BMJ* 2009 338 (Feb 12): p. b354
http://www.bmj.com/cgi/content/abstract/338/feb12_2/b354?ct=ct.
27. Jefferson T, Demicheli V, Rivetti D, Jones M, Di Pietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. *The Lancet* 2006; 367: 303-13. Published Online January 19 2006; DOI: 10.1016/S0140-6736(06) 67970-1.

28. Jefferson T, Del Mar C, Dooley L, Ferroni E, Al-Ansary LA, Bawazeer GA, van Driel ML, Foxlee R, Rivetti A. [Physical interventions to interrupt or reduce the spread of respiratory viruses: systematic review](#). BMJ. 2009 Sep 21;339:b3675. doi: 10.1136/bmj.b3675. Review.
29. World Health Organization. Pandemic influenza preparedness and response: a WHO guidance document. Geneva: WHO 2009. ISBN 978 92 4 154768 0.