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Peter Doshi
Are US flu death figures more PR than science?
BMJ 2005; 331: 1412 [Full text]

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Can we trust blindly the figures of CDC, RKI, etc.?

11 December 2005

Torsten Engelbrecht, journalist
20359 Hamburg

Send response to journal:
Re: Can we trust blindly the figures of CDC, RKI, etc.?

Peter Doshi's article "Are US flu death figures more PR than science?" is very revealing. It shows again that everybody who works with CDC figures and statements (journalists, scientists, etc.) has to ask him- or herself: Can I trust blindly the CDC's figures and statements - as well as the figures of other authorities of virus science? The point is that in Germany, for example, we have the same situation. The German pendant to the CDC, the Robert-Koch-Institut (RKI), states that last winter between 15,000 and 20,000 people in Germany died of viral flu (influenza). [1] But this statement is totally unfounded.

In fact, the statistics of the Germany's Federal Statistical Office differentiate between viral flus and non-viral flus. According to this statistic in 2004 there have been only 9 deaths caused by viral flu (influenza) (2003: 25; 2002: 10; 2001: 9), and 116 deaths caused by flus where viruses have not been found. Finally these 15,000 to 20,000 influenza deaths are pure estimates which are not disclosed as such estimates.

The same with the reporting data from hospitals in Germany. Also these report differentiate between influenza with virus proof and flu without virus proof. According to these statistics, in 2003 there have been 12 influenza deaths and 165 flu (without virus proof) deaths. And even if someone adds up all the figures (flu with and without virus proof) for the years 2000 till 2003, he or she gets just 350 deaths [2] - which is very far away from the 15,000 till 20,000 claimed by the RKI.

Moreover the RKI mentions the Arbeitsgemeinschaft Influenza (AGI) as source for its estimates. The AGI has been founded in 1991 by the pharmaceutical industry, and receives financial support by 4 vaccine makers. [3]

Torsten Engelbrecht www.torstenengelbrecht.com

[1] Robert-Koch-Institut, Influenza – Daten aus dem Saisonabschlussbericht 2004 / 2005 der AGI --> see

http://www.rki.de/cln_006/nn_387378/DE/Content/InfAZ/I/Influenza/Saison__04__05.html

[2] Koegel-Schauz, Angelika. Influenza-Viropoly. impf-report, Sept/Okt 2005, p. 7

[3] Arbeitsgemeinschaft Influenza. Was ist die AGI? --> http://influenza.rki.de/agi/index.html?c=about

Competing interests: None declared

Can we really trust CDC?

16 December 2005

Dr. Raj Mehta,
IT Consultant
Reginald S. Lourie Center for Infants and Young Chindren, 12301 Academy Way, Rockville, MD 20852, US

Send response to journal:
Re: Can we really trust CDC?

Peter Doshi's short article, "Are US flu death figures more PR than science?" is very interesting and important.

This is my initial response, will probably have more to say once I digest the implications of erroneous figures perpatrated by a public body like CDC.

There are major implications when the public body like CDC making such claims. Both professionals and the lay people take these figures and claims as gospel turth and base their actions on these statements. Such statements by CDC have a cascading and multiplying effect. Monies and time are spent to accommodate the conclusions of CDC. Which of course means for an organization (http://www.louriecenter.org) like the one I volunteer for, that something else which is important is not attended to.

This kind of twisting/misrepresentation of the facts, which for some ill advised reason CDC has embarked on, must brought to public attention.

I really laud Peter Doshi and your BMJ journal to have the courage to take up an issue which is not going to win friends at CDC.

I think more such efforts have to be undertaken by individuals and support to be given by Journal like yours to reverse the trend of twisting/misrepresentation of medical science data by both private and public bodies.

Thanks BMJ for publishing this item.

raj

Competing interests: None declared

Why do official statistics of "influenza deaths" underestimate the real burden?

2 January 2006

Udo Buchholz, Senior epidemiologist *Robert Koch Institute, Seestrasse 10, 13353 Berlin, Germany*, Torsten Schelhase (Federal Statistical Office), Walter Haas (Robert Koch Institute), Helmut Uphoff (State Health Department, Hessen)

Send response to journal:
Re: Why do official statistics of "influenza deaths" underestimate the real burden?

We would like to respond to the letter of Torsten Engelbrecht regarding deaths due to influenza in Germany. There are really two issues that need to be looked at separately: the first is the so called "official statistics" by death certificate, and the second is the method that is used to estimate the number of excess deaths in conjunction with influenza epidemics that seems to be discrepant with the first source. The two need to be interpreted in the context of their data sources and objectives of the analysis. The method for the aggregation of death data that is used by the Federal Statistical Office follows the WHO recommendation that asks countries to count the underlying condition, but not the immediate cause of death. For example: a person with diabetes that died of influenza will be counted as having died of diabetes. Testing for influenza is rarely done, for example because it has therapeutic consequences only if the test result is known within the first 48 hours after onset of symptoms. Testing a deceased person on autopsy to identify the cause of death is rather unusual and the proportion of those tested to all cases where symptoms would warrant such tests is small. Thus, very many deaths are "hidden" among other diseases. For those two reasons the number of "influenza deaths" that are given by the Federal Statistical Office only reflects the "number of times when a physician identified 'influenza' as the underlying cause of death and documented it on the death certificate". Obviously, this number will hardly represent the true number of influenza deaths.

Therefore, other methods are required to get a more realistic estimate of deaths due to (or associated with) influenza. The methods that are used (and published in international peer-reviewed journals) differ somewhat, but all have a similar principle. There is a baseline of deaths of all-causes (or “pneumonia and influenza”, as in the US) that usually has a seasonal pattern. In addition, however, it can be seen that during influenza epidemics there are peaks in all-cause mortality, and statistical methods try to estimate the difference of those peaks to the baseline. These methods are used internationally (1-4). Of course, there are limitations to this, for example it may be debatable if the death of a person with chronic obstructive pulmonary disease who died in the course of an influenza infection indeed died of influenza. Further, other concurrent epidemic diseases, such as those due to RSV, may lead to an overestimate of influenza associated deaths. These issues are usually discussed already in the same papers, or in accompanying critical and independent comments (5). It was pointed out by Doshi (6) that sometimes "flu deaths" are equated with "influenza associated deaths", and indeed we must be careful to always use correct terminology ourselves. In regard to Mr. Engelbrechts remaining comments we can state briefly that the method of our estimation has been peer reviewed and published in reference (4), and estimations for influenza associated hospitalizations follow the same logic as for influenza associated deaths. The

"Arbeitsgemeinschaft Influenza" (AGI) is a public-private partnership with the main goal to collect and disseminate data on seasonal influenza. As such, it is indeed supported by pharmaceutical companies (as clearly declared on its website), but the Robert Koch Institute that is responsible for scientific analysis of data receives no financial support other than from the government.

1. Serfling RE: Methods for current statistical analysis of excess pneumonia-influenza deaths. Public Health Rep 1963, 78:494-506.

2. Simonsen L, Clarke MJ, Stroup DF, Williamson GD, Arden NH, Cox NJ. A method for timely assessment of influenza-associated mortality in the United States. Epidemiology 1997, 8:390-5.

3. Clifford RE, Smith JW, Tillett HE, Wherry PJ: Excess mortality associated with influenza in England and Wales. Int J Epidemiol 1977, 6:115-128.4

4. Zucs P, Buchholz U, Haas W, Uphoff H. Influenza associated excess mortality in Germany, 1985-2001. Emerging Themes in Epidemiology 2005;21;2(1):6

5. Dushoff J: Assessing influenza-related mortality: Comment on Zucs et al. Emerging Themes in Epidemiology 2005, 2:7

6. Doshi P: Are US flu death figures more PR than science? BMJ 2005, 10.12.2005

Competing interests: None declared

Can we trust blindly the figures of CDC, RKI, etc.? Part 2

4 January 2006

Torsten Engelbrecht,
Journalist
20359 Hamburg

Send response to journal:
Re: Can we trust blindly the figures of CDC, RKI, etc.? Part 2

Dear sir, dear madam;

The RKI'S response "Why do official statistics of 'influenza deaths' underestimate the real burden?" is not an adequate answert to my Rapid Response message "Can we trust blindly the figures of CDC, RKI, etc.?" because it does not deliver the proofs neither for the claim that "official statistics of 'influenza deaths' underestimate the real burden" nor the answers to the fundamental questions:

- For example, the RKI claims that "very many [influenza] deaths are 'hidden' among other diseases. [Therefor]

the number of 'influenza deaths' that are given by the Federal Statistical Office only reflects the 'number of times when a physician identified 'influenza' as the underlying cause of death and documented it on the death certificate'. Obviously, this number will hardly represent the true number of influenza deaths." But (1) where is the proof that in these "hidden" cases a flu virus was the primary/sole cause of death? And (2) we must also ask: Where is the clear-cut proof that even the the number of 'influenza deaths' that are given by the Federal Statistical Office really reflects deaths caused primarily/solely by a flu virus?

- In this context the RKI may be so nice to deliver also the studies proving (1) the existence of respective flu viruses (showing photographs of the full genome and the virus casing), especially the one that according to the RKI caused 15,000 to 20,000 deaths in 2004/2005; (2) the studies proving clearly that these flu viruses - assuming they exist - are pathogenic (with a fatal potential); (3) studies proving that other factors/toxins can be excluded as possible/definite (primary or sole or contributing) cause of the deaths

- The RKI also states that its calculation methods are "internationally used" and "that in regard to Mr. Engelbrecht's remaining comment" it "states that the method of the estamation has been peer reviewed". But this does not deliver any kind of proof nor does it make sure that certain data can be taken for granted. In fact, there is good reason to say that peer reviewing is "slow, expensive, profligate of academic time, highly selective, prone to bias, easily abused, poor at detecting gross defects, and almost useless for detecting fraud", as for example former BMJ-editor Richard Smith outlined. [1], [2]

- It is also worth mentioning that I've sent a request to the RKI on Dec 13, 2005, asking (1)for the exact(!) calculation (mentioning all parameters) for the 15,000 till 20,000 deaths the RKI says are caused by a flu virus. But till today I haven't got any kind of such calculation. The study the RKI is mentioning in its RR message (Zucs P, Buchholz U, Haas W, Uphoff H. Influenza associated excess mortality in Germany, 1985-2001. Emerging Themes in Epidemiology 2005;21;2(1):6) refers only to the period of 1985 till 2001 (and not 2004/2005).

- In this context, the RKI let me know by e-mail that "due to lack of capacity" I couldn't expect an answer from them "before mid or end January". But one must wonder why the RKI needs so much time (one to one and a half months) to send me this exact calculation because actually the RKI should have it right at hand! (And by the way, the RKI has the capacity to deal with the issue, for example by puttting together a longer RR message.)

- As the RKI also mentions in its RR message, the published numbers of influenza deaths are "estimations". So in my mid December request I asked the RKI why the RKI does not outline the numbers as estimations in its official statements. And the RKI answered: "It is often being mentioned" that the numbers are about estimations. But till today (though having asked for it several times) I haven't received any press release or other (important)

document from the RKI in which it is being mentioned that the influenza death numbers are about estimations. In fact, in very important official documents/press relaeses like on the website of the RKI it is not being mentioned. [3], [4] Also in this case, one must wonder why the RKI is not able to deliver documents the RKI should have right at hand!

- At the end of its RR message the RKI says that "The 'Arbeitsgemeinschaft Influenza' (AGI)... is indeed supported by pharmaceutical companies..., but the RKI that is responsible for scientific analysis of data receives no financial support other than from the government." But what does the RKI wants to tell us with this statement? If the RKI fully relies on an institution which is paid by the pharmaceutical industry, how can the RKI guarantee that the data coming from the AGI and being published by the RKI is absolutely unbiased?

- Moreover, the RKI may be so nice disclosing in detail all kinds of payments (lecture honorariums, research funding, etc.) the scientists, working for the RKI or the insitutions directly connected with and/or integrated into the RKI, receive. For example, the German "Steady Vaccination Commission" ("Ständige Impfkommission"; STIKO) is part of the RKI-system. And the STIKO's chairman, Prof. Heinz-J. Schmitt, is memeber of the board of directors of the STIKO [5] which is being supported by the pharmaceutical companies Glaxo SmithKline and Chiron-Behring. [6] And Schmitt is also adviser of the Glaxo SmithKline facility "Gesundes Kind" ("Healthy Child"). [7] How it is being assured that these connections do not cause conflicts of interests affecting the impartiality of the scientist (of science)?

Torsten Engelbrecht

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[1] Judson, HF. The Problems of Peer Review, in: The Great Betrayal. Fraud in Science. Harcourt, 2004, p. 244-286

[2] Engelbrecht, Torsten. "The Industry Exerts Pressure", interview with former NEJM-editor Marcia Angell on editorial autonomy, fraud in science and the purpose of peer reviewing. message, July 2005, p. 66-69; see http://www.torstenengelbrecht.com/artikel_medien/message_Angell_English.pdf

[3] RKI. Influenza – Daten aus dem Saisonabschlussbericht 2004/2005 der AGI. RKI-website; see http://www.rki.de/cln_006/nn_226464/DE/Content/InfAZ/I/Influenza/Saison__04__05.html

[4] RKI. Influenza-Schutzimpfung jetzt! Press release of the RKI and the Paul Ehrlich-Institut; see

http://www.rki.de/cln_011/nn_226574/DE/Content/Service/Presse/Pressemitteilungen/2004/25__04.html

[5] Website of the foundation "Präventive Pädiatrie"; see http://www.stiftung-praeventive-paediatrie.de/ueberuns.html

[6] Website of the foundation "Präventive Pädiatrie"; see http://www.stiftung-praeventive-paediatrie.de/kooperation.html

[7] Website of "Gesundes Kind; see http://www.gesundes- kind.de/gsk/home/impressum.htm

Competing interests: None declared

US Flu Mortality Estimates Are Based on Solid Science

11 January 2006

Lone Simonsen, Robert Taylor, Cecile Viboud, Jonathan Dushoff, and Mark Miller
National Institutes of Health, Bethesda, MD 20892

Send response to journal:
Re: US Flu Mortality Estimates Are Based on Solid Science

In his recent commentary" Are US flu death figures more PR than science?[1],"Peter Doshi argues that CDC uses inappropriate statistical models to deliberately exaggerate its estimates of influenza-related mortality. Not so. Researchers argue about many things when it comes to influenza epidemiology, but the need to use statistical methods to measure the total mortality impact is not one of them. In fact, statistical methods have been used to estimate the mortality burden of influenza for decades, have been extensively vetted in the scientific literature, and are quite robust.

Epidemiologists rely on these statistical models because the International Classification of Diseases (ICD) code for influenza deaths severely undercounts the true number of deaths related to influenza[2]. This is partly because influenza is rarely confirmed in the laboratory and partly because people are far more likely to die from secondary bacterial pneumonia or exacerbations of underlyingchronic diseases than from primary influenza pneumonia. To top it off, procedures to assign a single underlying cause of death strongly favor chronic conditions over acute infectious disease. The classic approach to overcome this problem is the Serfling regression model, which measures excess mortality abovean expected winter baseline [3],[4],[5].Methods based on a regression model guided by virus surveillance data have beendeveloped more recently[6],[7].All these approaches yield similar estimates of the average seasonal US influenza mortality burden when applied to the same time period (Table). Moreover, the deaths identified by the models only occur when influenza epidemics occur and are larger in influenza seasons dominated by severe A(H3N2)viruses[8]. The important point is that regardless of what is recorded on death certificates, the deaths identified by the models would not have occurred in the absence of

influenza.

Doshi specifically questions why the current CDC estimate of influenza-related deaths is much higher than the former estimate of 20,000 deaths[4]. The disparity is simply a consequence of studying different time periods and the large variability between seasons. The earlier estimate was based on data from 1972-1992, while the more recent estimate was based on data from 1976-1999; the latter period included a higher frequency of severe influenza A(H3N2) seasons, and, most importantly, the proportion of very elderly people quadrupled by the end of the 1990s. The table illustrates that similar estimates obtain when the various models are applied to the same time periods, and that population aging explains much of the increase over the last decades. The reason why population aging is so influential is that the influenza-related mortality risk increases exponentially in the last decades of life, with the result that the rapidly growing subset of very elderly people over 85 years bears adisproportionate, substantial and growing share of the mortality burden[5,6.]

Doshi further wonders why the number of deaths in the 1968 pandemic season is lower than the average forrecent seasons. Again, because of population aging one cannot compare crude estimates over several decades. After we adjusted for the effect of aging, the estimate of ~35,000 deaths associated with the mild 1968 pandemic was actually exceeded by a few more recent severe A(H3N2) seasons[5] . Nonetheless, the 1968 pandemic stands out because of a profound mortality age shift, so that nearly half of all the deaths were in persons under age 65. In contrast, only about 10% of deaths associated with more recent influenza seasons are inpersons under 65[5]

In conclusion, estimates of the mortality burden of influenza are not "a mess," as Doshi states, but rather represent the best assessments we have. We suspect Doshi is not the only one towonder about the science behind influenza mortality estimates, and we hope our response here has helped to set minds at ease.

But Doshi's suggestion that CDC deliberately exaggerates influenza mortality for the benefit of the pharmaceutical industry while the rest of the scientific community stands by, meek and mute, is absurd. It might have been more illuminating had BMJ published a counterpoint from an expert in the field simultaneously with Doshi's article, the better to avoid confusion and needless damage to public health efforts.

Table. Average seasonal estimates ofinfluenza-related deaths for specific time periods, based applying variousmodels to all USdeaths.

		1972-1992	1976-1999	1990-1999
Crude estimates of all-cause excess mortality				
Former CDC Serfling model[4]		20,000		
Current CDC virus-guided model[6]*	-	-	34,470	51,203
NIH Serfling model[5]		24,400	33,400	48,700
Annual regression model[7]				51,900
Age-adjusted estimates of all-cause excess mortality**				
NIH Serfling model[5]		19,800	23,600	30,800

* Crude all-cause excess deaths fromtable 2 and 3 in reference 6

** These estimates were carefully adjustedfor population aging, but not for the increased circulation of virulent A(H3N2)viruses in the 1990's – a factor that explains much of the residual increasecompared to the previous time periods[5].

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[1] Doshi P. Are US flu death figuresmore PR than science? BMJ (2005) 331:1412.

[2] Barker WH, Mullooly JP. Underestimation of the role of pneumonia andinfluenza in causing excess mortality. Am J Public Health. (1981); 71(6):643-5.

[3] Serfling RE.Methods for current statistical analysis of excess pneumonia-influenzadeaths. Public Health Rep. (1963);78:494-506.

[4] Simonsen L, Clarke MJ, Williamson GD, Stroup DF, Arden NH,Schonberger LB. The impact of influenzaepidemics on mortality: introducing a severity index. Am J Public Health. (1997); 87:1944-1950.

[5] Simonsen L, Reichert T, Viboud C, Blackwelder WC,Taylor RJ, and Miller MA. Impact of influenza vaccination on seasonal mortalityin the USelderly population. Arch Intern Med.(2005); 165(3):265-72.

[6] Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza andrespiratory syncytial virus in the United States. JAMA (2003); 289: 179-186.

[7] Dushoff J, Plotkin JB, Viboud C,Earn DJD, and Simonsen L. Mortality due to Influenza in the United States—AnAnnualized Regression Approach Using Multiple-Cause Mortality Data. Am. J.Epidemiol. (2006); 163:181-187.

[8] Reichert TA, Simonsen L, Sharma A, Pardo SA, FedsonDS, Miller MA.. Influenza and the winter increase in mortality in the UnitedStates, 1959-99. Am J Epidemiol. (2004); 160(5):492-502.

Competing interests: None declared

The Peril of Correlation

14 January 2006

David R. Crowe,
President, Alberta Reappraising AIDS Society
2636 Toronto Cresc., NW, Calgary, AB, T2N 3W1, Canada
Send response to journal:
Re: The Peril of Correlation

The influenza virus just don't get no respect, at least according to its afficionados at the RKI and CDC. There are many flaws with their argument, however, that 'surplus' deaths at times when flu is common are due to the flu. There may be a correlation, but there may not be causation.

Epidemics of respiratory disease tend to occur in winter months, making the weather a plausible confounding factor. Winter conditions vary from year to year, and bad winters will increase the use of fossil fuels, and will result in automobiles being driven in cold weather more often, resulting in less efficient combustion. People will also spend more time indoors.

The Zucs et al analysis of excess mortality in Germany cited by RKI (1) ignores any such non-infectious factors that might lead to the increased deaths. The definition of 'flu seasons' as an excess incidence of doctor visits and hospitalizations due to acute respiratory 'infections' (in the absence of testing for viral causation in the vast majority of cases) leads to a tautology. More illness will almost certainly be associated with more deaths, but there is no proof that the excess deaths are due to the flu or infectious diseases. Just calling it an 'Influenza Season' does not make it one.

Furthermore, the choice of samples by private physicians performing surveillance for the RKI are not random (1). The perception of doctors that there is a lot of flu around might well be influenced by newspaper reports and the RKI itself, perhaps even by the weather. This might lead to the submission of more samples, resulting in an amplification of concern.

That there might be a hidden epidemic of pollution-induced respiratory disease is plausible when we consider that Dr. Peter Joseph of the University of Pennsylvania found higher levels of MTBE (an oxygenate) mixed into gasoline in Philadelphia in the winters of the early 1990s was associated with large increases in physician visits for a variety of respiratory conditions, including upper respiratory infections (compared with earlier years and

summers, when rates of MTBE in gasoline are lower). Rates of other conditions did not change dramatically. (2) Changes in the formulation of gasoline are easily overlooked. But the Philadelphia study shows that they may have a large impact on human health, especially when combined with weather factors (e.g. higher or lower winds than normal, temperature inversions, extremely low temperatures).
The German excess mortality study (1) does not consider any environmental causes for peaks in mortality, particularly in the winters of 1989/90 and 1995/96. Information on air quality factors such as SO_2, CO, O_3, NO_2 and other common air pollutants (3) (4) should have been included in a multi-variate analysis.
Flu scientists have no qualms about claiming that their favourite virus is really the underlying cause responsible for the deaths of many people with certificates stating bacterial pneumonia, but they seem loath to consider that upper respiratory tract infections (if they are even infections at all) could have a non-infectious underlying cause.

1. Zucs P, Buchholz U, Haas W, Uphoff H. Influenza associated excess mortality in Germany, 1985-2001. Emerging Themes in Epidemiology 2005;21;2(1):6.
2. Joseph PM et al. Visits to physicians after the oxygenation of gasoline in Philadelphia. Arch Environ Health. 2002 Mar-Apr; 57(2): 137-54.
3. What causes air pollution? UK National Air Quality Information Archive. http://www.airquality.co.uk/archive/what_causes.php
4. Six Principal Pollutants. US Environmental Protection Agency. http://www.epa.gov/ airtrends/sixpoll.html

Competing interests: None declared

Author's reply

16 January 2006

Peter Doshi,
graduate student
Harvard University
Send response to journal:
Re: Author's reply

I thank authors Simonsen, Taylor, Viboud, Dushoff, and Miller from the National Institutes of Health for their letter of 11 Jan 2006.[1] I think we all share the goal of improving and protecting the public's health, and respond in that spirit.
Simonsen et al. raise a number of issues in contention with my paper,[2] but, importantly, only quote two words of mine and do not address my paper's major criticisms: namely, that the rationale behind the supposedly unique relationship between flu and pneumonia is questionable; that the CDC's estimates of an 80% increase from 20,000 to 36,000 influenza-associated deaths are not supported by a 30% decrease in recorded flu deaths over the same period; that CDC continues to misrepresent its estimates of influenza-associated mortality as recorded flu deaths.[3]
Below, I will address the concerns of Simonsen et al. seriatim.
Simonsen et al. write, "Doshi argues that CDC uses inappropriate statistical models to deliberately exaggerate its estimates of influenza-related mortality." I made no such claim. Rather, I address the significant statistical

incompatibilities between official estimates and national vital statistics data. Concerning the inappropriateness of the CDC's model,[4] this is in fact something Simonsen et al. argued in 2003: "We propose that rigorous demonstrations of validity and benefit precede adoption of this new modeling approach."[5]

Simonsen et al. state: "Researchers argue about many things when it comes to influenza epidemiology, but the need to use statistical methods to measure the total mortality impact is not one of them." This misses the point, for it is not what I argued. My paper documents defects within the statistics (biased assumptions, contradictory data)--not against the use of statistics.

Simonsen et al. claim that statistical methods "are quite robust", but where are the means by which the figures can be verified as true and the methods can be validated? Indeed, claims of robustness obscure Dushoff's own analysis that gauging the true impact of influenza remains controversial.[6] He pointed out that some researchers[7] argue flu viruses "trigger only a small minority" of seasonal excess deaths in temperate countries.

To explain why estimates of influenza mortality rose between the 1980s and 1990s, Simonsen et al. cite "a higher frequency of severe influenza A(H3N2) seasons, and, most importantly, the proportion of very elderly people quadrupled by the end of the 1990s." The CDC has offered similar explanations (with the difference being that the CDC cites the growing 65+ population, not 85+), but these claims are equally hard to support.

Simonsen et al. do not specify what the 85+ population is being compared to, but I will assume it is in proportion to the 65+ age group. Population data show the 85+ subset occupied 8% of the total 65+ population over the 1970s, 9% over the 1980s, and 11% over the 1990s.[8,9] Proportional increases are thus far short of the claimed quadrupling. Also troubling is the CDC's and Simonsen et al.'s claim of a higher frequency of severe flu seasons in the 1990s. As I documented in my paper, there were 30% fewer recorded flu deaths over the 1990s than the 1980s, a fact that does not support the claim of more severe flu seasons.

Simonsen et al.'s discussion of the 1968-69 flu season helps explain what made it different from ordinary flu seasons. In doing so, they confirm that the annual (ie. non-pandemic) flu can be more deadly than a pandemic: "the mild 1968 pandemic was actually exceeded by a few more recent severe A(H3N2) seasons." Their position, however, is at odds with the mass media, which promotes the notion that pandemic flu means, in a word, death.[10,11,12] It is also at odds with the CDC: "Past influenza pandemics have led to high levels of illness, death, social disruption, and economic loss."[13]

"In conclusion," write Simonsen et al., "estimates of the mortality burden of influenza are not 'a mess,' as Doshi states, but rather represent the best assessments we have." If Simonsen et al. are referring to the official CDC model as one of "the best assessments we have", it seems difficult to reconcile considering their previous stance which rejected adoption of the new model.[5] It is also difficult to reconcile with JAMA's published follow-up responses, which all criticized the CDC's new modeling methodology.[5,14,15]

Simonsen et al. clarify that many of the statistical models "yield similar estimates". Many models also make similar questionable assumptions; it is not enough to judge by the similarity of results. My paper focuses on the CDC's model because this particular model heavily impacts mass media and policy decisions. This is a model that estimated 51,296 influenza-associated deaths in the 1997-98 flu season [4] a season the Washington Post called

"mild to moderate" at the time.[16] Is this one of the models that Simonsen et al. is calling "the best assessents we have"?

Finally, Simonsen et al. declare: "Doshi's suggestion that CDC deliberately exaggerates influenza mortality for the benefit of the pharmaceutical industry while the rest of the scientific community stands by, meek and mute, is absurd." Accusations need to be substantiated with evidence. A direct quote would have been helpful, but hard to find since I never made such claims. What I did relate was evidence that the CDC advocates that "medical experts ... predict dire outcomes" from the flu for the stated purpose of generating demand for flu vaccination.[17] My article does not deal with speculation over motivation, but facts and objective inconsistencies.

I was surprised to read Simonsen et al.'s suggestion that publication of my paper caused "needless damage to public health efforts." In my opinion, no risk to public health can be greater than the one produced by relying on faulty data, statistics, or analysis. Public health efforts and policy must rely on consistent, evidence-based statements as well as transparent communication with the public.

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Competing interests: None declared

Are estimates of influenza-associated deaths in the US really just PR?

18 January 2006

William W Thompson, Epidemiologist
US Centers for Disease Control and Prevention, Atlanta, GA, 30333,
David Shay, Eric Weintraub, Lynnette Brammer, Martin Meltzer, Nancy Cox, Joe Bresee
Send response to journal:
Re: Are estimates of influenza-associated deaths in the US really just PR?

In the 10 December 2005 BMJ, Mr. Doshi states that estimates of influenza-associated mortality made by the U.S. Centers for Disease Control and Prevention (CDC) are flawed, and he suggests that they are deliberately exaggerated in order to increase the use of influenza vaccine. The author has misunderstood the methods used to estimate influenza-associated deaths, and made several errors of fact we would like to correct.

He correctly notes that estimates of U.S. deaths associated with the 1968-9 influenza A(H3N2) pandemic total 34,000 people [1], while current annual estimates of influenza-associated mortality are ~36,000. [2] He suggests that these estimates do not make sense, and he states that a pandemic must result in more deaths than an average inter-pandemic influenza season. This is not true because pandemics, like interpandemic influenza seasons, vary in severity, by the age groups most affected, the size of the populations affected and in their length. Therefore, it cannot be assumed a priori that pandemics will cause more mortality than interpandemic seasons. The author should be reminded that the 1968-9 pandemic was not particularly severe, with lower rates of mortality compared with both the 1918 and the 1957-8 pandemics. Leading influenza experts have postulated that reduced mortality during the 1968-9 pandemic may have been due to pre-existing population immunity to the N2 neuraminidase of the pandemic virus. Since the last pandemic, ~90% of all influenza-associated deaths have occurred among those aged >65 years. Risk is not constant among the elderly. Those aged >85 years are 19 times more likely to suffer from an influenza-associated respiratory and circulatory death compared with persons aged 65-69 years. [3] The steady aging of the U.S. population along with the predominance of A(H3N2) seasons during the 1990's (i.e., six of the nine season were A(H3N2) predominant seasons) and the increasing length of the influenza seasons [2;4] have all contributed to the current estimates, with more influenza- associated deaths occurring during annual influenza seasons than during the 1968-9 pandemic.

Mr. Doshi suggests that the 12% increase among U.S. residents aged >65 years from 1990 through 2000 indicates the aging of the population could not be responsible for a significant increase in influenza- associated deaths. However, an earlier estimate of 20,000 annual influenza -associated deaths was made using data from

1972 through 1992 [5], while our more recent estimate of 36,000 annual deaths is derived from an analysis of deaths from 1990-1999. (2) From 1972 through 1999, the number of persons aged >65 years increased 64% and the number of persons aged >85 years more than doubled. [6] Thus, the rapid aging of the US population between these periods can indeed explain, in part, why influenza-associated deaths have increased.

We estimate that ~36,000 influenza-associated deaths occurred from the 1990-91 through the 1998-99 influenza seasons among those with an underlying cause of death listed as a respiratory or a circulatory disease. Of these deaths, we estimate that ~8100 occurred among those with an underlying cause of death categorized as pneumonia and influenza. Thus, pneumonia and influenza deaths are a subset of respiratory and circulatory deaths. Influenza may precipitate deaths from other causes, such as cardiovascular diseases, as first appreciated during the 1957-8 pandemic. [7] It has been recognized for many years that influenza is infrequently listed on death certificates [8] and testing for influenza infections has been rare, particularly among the elderly at greatest risk. In addition, some deaths, particularly in the elderly, are associated with secondary complications of influenza (including bacterial pneumonias). For these reasons, statistical modeling strategies have been used to estimate influenza associated deaths for many decades, both in the United States and the United Kingdom [2;5;9-13]. It is also important to recognize the variability of influenza seasons; during the period over which 36,000 annual deaths were estimated, on average, the range in annual estimates was from 17,000 to 51,000 deaths.

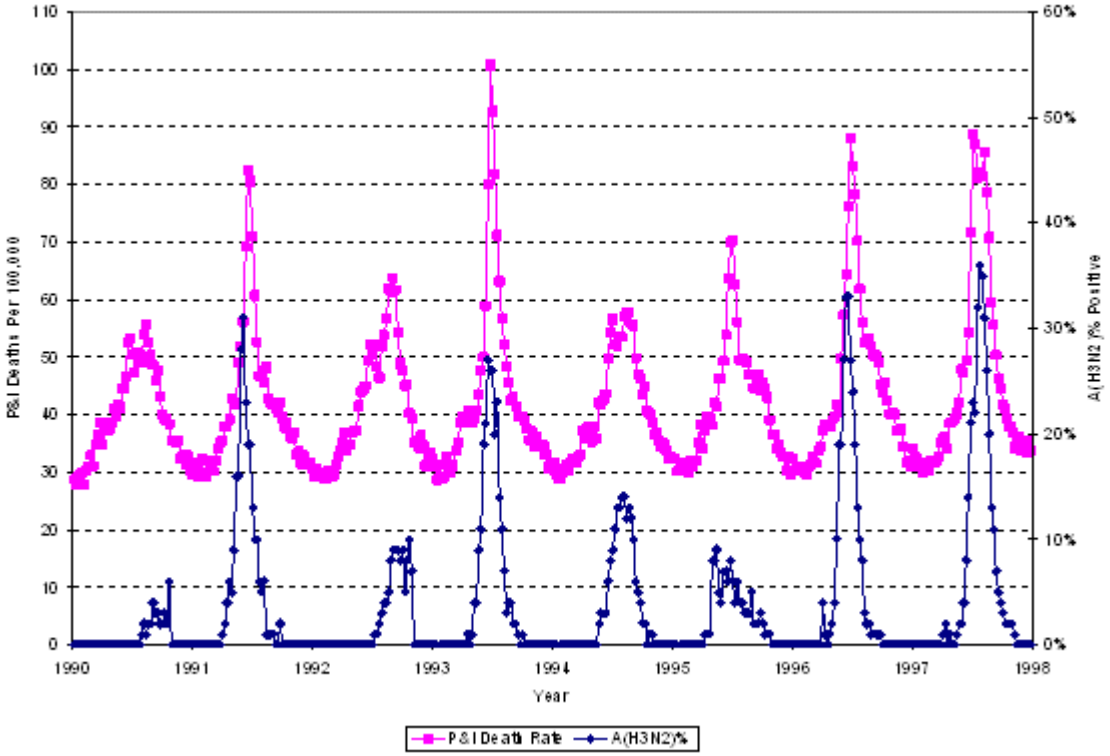
Contrary to the suggestion that the number of influenza-associated deaths has been exaggerated, CDC's models provide a conservative estimate of such deaths. Our estimate of 36,000 influenza-associated deaths with an underlying respiratory or circulatory cause represents <3% of all these deaths. We control for seasonal variations in deaths and for the circulation of respiratory syncytial virus, a viral pathogen that has increasingly been recognized as an important cause of wintertime morbidity and mortality. [14] The consistent relationship between the circulation of influenza and weekly peaks in mortality is impossible to ignore, explaining the decades of research using statistical methods to estimate influenza mortality.

Finally, Dr. Rosenthal of Harvard University Health Services is quoted as suggesting that individuals infected with influenza die of secondary bacterial pneumonias, and not viremia. We agree that individuals infected with influenza typically do not die of viremia. Isolation of human influenza viruses in the blood has been reported only rarely. [15] However, elderly individuals in particular are at risk of serious morbidity from bacterial pneumonias and many other direct and indirect complications after influenza infections. Furthermore, a recent report documented that 153 children died with laboratory-confirmed influenza virus infections in the United States during the 2003-04 influenza season. [16] Approximately half of these children did not receive a clinical or autopsy diagnosis of pneumonia. Their deaths may have resulted from direct effects of viral pathogenicity, host responses to infection, or a combination of factors, including exacerbation of a variety of underlying conditions, including chronic neurologic diseases. [17]

We stand by our estimate that during recent influenza seasons, approximately 36,000 influenza-associated deaths occur annually in the United States. Similar estimates were published by the National Institutes of Health

and academic investigators using different statistical methods.[2;13] Influenza remains the most important cause of vaccine- preventable deaths in the United States. Developing improved prevention strategies for influenza depends on reasonable and well-documented disease burden estimates. We encourage constructive dialogue on how best to refine these estimates.

Figure 1. Pneumonia and Influenza Death Rates and Percent of Samples Positive for Influenza A(H3N2) viruses by Week in United States, 1990-1998



William W. Thompson, David K. Shay, Eric Weintraub, Lynnette Brammer, Martin Meltzer, Nancy J. Cox, and Joseph S. Bresee, US Centers for Disease Control and Prevention, Atlanta, GA 30333.

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Competing interests: None declared

Author's reply #2

22 January 2006

Peter Doshi,
graduate student

I thank Thompson, Shay, Weintraub, Brammer, Meltzer, Cox, and Bresee from the U.S. Centers for Disease Control and Prevention for their letter of 18 Jan [1] and I am happy to note their interest in engaging in

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Re: Author's reply #2

constructive dialogue. I also want to thank Engelbrecht,[2] Mehta,[3] and Crowe,[4] whose letters raise additional concerns regarding the reliability and basic assumptions of current official U.S. (and German[5]) estimates of influenza-associated mortality.

While Thompson et al. (CDC) and Simonsen et al. (NIH) are both critical of my paper, neither address my article's[6] major criticisms. For clarity, I will summarize them here: First, the rationale behind the supposedly unique relationship between flu and pneumonia is questionable; Second, the CDC's estimates of an 80% increase from 20,000 to 36,000 influenza-associated deaths are not supported by a 30% decrease in recorded flu deaths over the same period (table); Third, the CDC continues to misrepresent its estimates of influenza-associated mortality as recorded flu deaths.[7]

Thompson et al. state that I "made several errors of fact," but do not quote my paper to document which of my statements, if any, were inaccurate. In addition, Thompson et al. write that "[Doshi] suggests that they [the death figures] are deliberately exaggerated in order to increase the use of influenza vaccine." I made no such claim, and debate over motivations only serves to sidetrack this discussion. Rather, I referenced flu shot campaign literature which shows that current statistics are being leveraged to increase flu vaccination.[8]

There has been much discussion regarding the question of whether population figures support the CDC's increases in flu-associated death estimates. The CDC's "Influenza Model" (shown in Table 2 in their paper[9]) estimated an average of 18,715 annual flu-associated deaths occurred during the 1980s. (This figure supports the previous official estimate of 20,000.[10]) For the 1990s, their model estimated 35,271 annual deaths.

Thompson et al. state that the 65+ population increased 64% and 85+ population has "more than doubled" from 1972 to 1999 and "can indeed explain, in part, why influenza-associated deaths have increased." However, it is only logical to compare rising flu-associated mortality estimates with population data over the same time period--the 1980s to 1990s. Here, without further, model-independent ways to ascertain and verify the risk of flu-associated death across all age groups, it remains undetermined and implausible that the population increases are sufficient to explain the 88% rise in CDC estimates. (See table.)

Table: Yearly averages over the 1980s and 1990s.

	1980s	1990s	Percent
Current CDC model, estimated	18,715	35,271	88%
Recorded flu deaths, all ages[11]	1702	1197	-30%
Population, 65+[12]	28,165,119	33,472,890	19%
Population, 85+[12]	2,622,438	3,667,187	40%

Population, 85+[12]	2,622,438	3,667,187	40%
Proportion, 85+ to 65+	0.09	0.11	18%

Thompson et al. ask for dialogue "on how best to refine these [CDC] estimates." One suggestion would be to correct the widespread misrepresentation of statistical estimates of flu-associated mortality as recorded flu deaths. In their letter, German officials voiced the need to "always use correct terminology",[5] and I think much can be gained from this advice. A second suggestion would be to make clear to the public the assumptions built into the CDC model, as well as the dangers such assumptions portend. For example, the basic assumption that influenza is responsible for the majority of seasonal excess deaths is controversial,[13] and weekly regression analyses, as Simonsen et al. pointed out, "are in danger of being confounded by other seasonal factors."[14]
I think discussion would be best served by focusing attention back to the questions regarding the statistical inconsistencies in official flu-associated mortality estimates.
Peter Doshi

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Competing interests: None declared

How useful are flu vaccines?

25 January 2006

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Researcher
University of Perugia, 06123, Italy
Send response to journal:
Re: How useful are flu vaccines?

Thompson et al. [1] highlight the correlation between "pneumonia and influenza" estimated death rates and the percentage of samples positive for influenza A(H3N2) viruses by week in United States from 1990 to 1998 (cf. Fig. 1, [1]). This correlation is not in itself inconsistent with the hypothesis that other factors might substantially or even predominantly contribute to the mortality seasonal burden. Apart from the respiratory illnesses caused by the increase of environmental pollutants during the winter season [2], it is worth remembering that "Cold weather alone causes striking short term increases in mortality, mainly from thrombotic and respiratory disease", even without an influenza epidemic [3].
This is in agreement with the generally recognized circumstance that "isolation of human influenza viruses in the blood has been reported only rarely"[1] and that the immediate cause of death in almost all cases is not the viral infection itself but an indirect "complication", like secondary bacterial pneumonia.
That there is a serious problem here for the conventional estimates of the "pneumonia and flu" death rates is widely accepted. For instance, one member of the Simonsen et al. team, Jonathan Dushoff, published a few months ago a useful note emphasizing: "Approaching a consensus on the health and mortality burden of influenza, and on the cause of winter excess mortality in general, is an important scientific and public policy goal. For this to happen, further progress is needed in several areas", and concluding: "The contribution of influenza to morbidity and mortality – and, more broadly, cataloging the causes of daily and season excess deaths and hospitalizations – remain as unresolved questions with important scientific and public-health implications." ([4])
More should be done in the way of epidemiological research to assess the relative weight of all plausible factors and to ascertain how frequently the flu viruses are actually involved in the fatal outcomes. Most importantly, it must be pointed out that the so-called "complications" are also linked to influenza-like illness (ILI), which is "clinically indistinguishable from influenza" [6]. ILI, defined as a symptomatic syndrome, is in fact caused by

hundreds of different agents, including RSV (respiratory syncytial virus), picornaviruses, parainfluenza, hMPV (human metapneumovirus), coronaviruses etc.(see e.g. [5]).

Now, an important public health issue arises at this point, since vaccine is protective only against two of the agents causing symptomatic, clinical flu. It follows that even if clinical flu were the underlying cause of seasonal differences in "pneumonia and influenza" death rates, this would not in itself provide a solid ground for the mass flu vaccination campaigns.

It is interesting that Doshi's critics ([1], [9]) seem to evade the crucial issue of the extent the flu vaccines are succeeding in preventing clinical flu. The results of two recent meta-analyses are by no means encouraging ([6], [7]). In [6], which deals with 65+ individuals (one of the high priority groups for mass vaccination according to the CDC), it is stated that "the usefulness of vaccines on the community [as opposed to long-term care facilities] is modest"; in [7] the effectiveness of vaccines in children younger than 2 (inactivated vaccines) or older than 2 (both inactivated and live attenuated vaccines) was found to be "low". One of the main reasons given to explain these disappointing results is that "vaccines are specifically targeted at influenza viruses and are not designed to prevent other causes of influenza-like illness"[7].

In an interview the senior author of [6] and [7], Dr. Tom Jefferson, put the issue in a refreshingly explicit way: "The vaccine doesn't work very well at all. [...] Vaccines are being used as an ideological weapon. What you see every year as the flu is caused by 200 or 300 different agents with a vaccine against two of them. That is simply nonsense."[8]

So it appears that the picture, not only at a theoretical level but even as regards "public health efforts"[9], is much more complicated than that provided by the NIH and CDC representatives.

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Competing interests: None declared