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FEATURE

INFLUENZA

Influenza: marketing vaccine by marketing disease

The CDC pledges "To base all public health decisions on the highest quality scientific data, openly and objectively derived." But **Peter Doshi** argues that in the case of influenza vaccinations and their marketing, this is not so

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Promotion of influenza vaccines is one of the most visible and aggressive public health policies today. Twenty years ago, in 1990, 32 million doses of influenza vaccine were available in the United States. Today around 135 million doses of influenza vaccine annually enter the US market, with vaccinations administered in drug stores, supermarkets—even some drive-throughs. This enormous growth has not been fueled by popular demand but instead by a public health campaign that delivers a straightforward, who-in-their-right-mind-could-possibly-disagree message: influenza is a serious disease, we are all at risk of complications from influenza, the flu shot is virtually risk free, and vaccination saves lives. Through this lens, the lack of influenza vaccine availability for all 315 million US citizens seems to border on the unethical. Yet across the country, mandatory influenza vaccination policies have cropped up, particularly in healthcare facilities,[1] precisely because not everyone wants the vaccination, and compulsion appears the only way to achieve high vaccination rates.[2] Closer examination of influenza vaccine policies shows that although proponents employ the rhetoric of science, the studies underlying the policy are often of low quality, and do not substantiate officials' claims. The vaccine might be less beneficial and less safe than has been claimed, and the threat of influenza appears overstated.

Now we are all "at risk" of serious complications

Influenza vaccine production has grown parallel to increases in the perceived need for the vaccine. In the US, the first recommendations for annual influenza vaccination were made in 1960 (table1).⇓ Through the 1990s, the key objective of this policy was to reduce excess mortality. Because most of influenza deaths occurred in the older population, vaccines were directed at this age group. But since 2000, the concept of who is "at risk" has rapidly expanded, incrementally encompassing greater swathes of the general population (box 1). As one US Centers for Disease Control and Prevention (CDC) poster picturing a young couple warns: "Even healthy people can get the flu, and it can be serious."[3] Today, national guidelines call for everyone 6 months of age and older to get vaccinated. Now we are all "at risk."

Not to worry: officials say influenza vaccines save lives

Risk of serious illness is a problem—but, according to the official narrative, a tractable problem, thanks to vaccines. As another CDC poster, this time aimed at seniors, explains: "Shots aren't just for kids. Vaccines for adults can prevent serious diseases and even death."[11] And in its more technical guidance document, CDC musters the evidence to support its case. The agency points to two retrospective, observational studies. One, a 1995 peer-reviewed meta-analysis published in *Annals of Internal Medicine*, concluded: "many studies confirm that influenza vaccine reduces the risks for pneumonia, hospitalization, and death in elderly persons during an influenza epidemic if the vaccine strain is identical or similar to the epidemic strain."[12] They calculated a reduction of "27% to 30% for preventing deaths from all causes"—that is, a 30% lower risk of dying from any cause, not just from influenza. CDC also cites a more recent study published in the *New England Journal of Medicine*, funded by the National Vaccine Program Office and the CDC, which found an even larger relative reduction in risk of death: 48%.[13]

If true, these statistics indicate that influenza vaccines can save more lives than any other single licensed medicine on the planet. Perhaps there is a reason CDC does not shout this from the rooftop: it's too good to be true. Since at least 2005, non-CDC researchers have pointed out the seeming impossibility that influenza vaccines could be preventing 50% of all deaths from all causes when influenza is estimated to only cause around 5% of all wintertime deaths.[14 15]

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Box 1. A policy without an objective

Despite the enormous sums of money spent fighting the perceived threat of influenza, there are surprisingly few instances of unambiguous statements describing the objectives of influenza vaccination policy. Here is a sampling, drawn from more than five decades of influenza vaccination policies in the United States, that demonstrates the changing purpose of the campaign—from one with a clear objective of saving older people's lives, to one without any stated objective.

In 1964, four years after annual influenza vaccination policies were first instituted, CDC influenza branch chief Alexander Langmuir and colleagues wrote that the recommendation "was based on three broad assumptions: 1. That excess mortality was the most important consequence of epidemic influenza. 2. That polyvalent virus vaccines had been at least partially effective in preventing clinical illness during most epidemics and therefore presumably would reduce the risk of death among the aged and chronically ill. 3. That epidemics cannot be predicted with sufficient accuracy to permit confident planning of control measures on a year to year basis."[4] In 1984, recommendations from the Advisory Committee on Immunization Practices stated: "Because of the increasing proportion of elderly persons in the United States and because age and its associated chronic diseases are risk factors for severe influenza illness, the future toll from influenza may increase, unless control measures are used more vigorously than in the past. . . . For about 20 years, efforts to reduce the impact of influenza in the United States have been aimed primarily at immunoprophylaxis [vaccination] of persons at greatest risk of serious illness or death."[5] Today, the recommendations do not even mention the effect the policy aims to achieve.[6]

Box 2: Deciphering the numbers

As concern surged this January over a worse than usual influenza season, members of the media seemed unsure whether the CDC's announcement that "vaccine effectiveness (VE) was 62%"[7] represented good versus disappointing news.[8]

NBC anchor Brian Williams: "I worry about this number. I woke up to reports of this number. It can disincentivize people to go get that flu shot which all of you are saying is still so important."

Chief medical editor Nancy Snyderman: "And I had the same concern when you see 62%, because I'm afraid people will say 'well, it's half and half.' But remember, if you have a 62% less chance of getting of getting the flu, it means less chance of being on antibiotics, less chance of ending up in an intensive care unit, and as we've seen from this uptick in numbers, 62% less chance of dying."[9]

Although the study never tested more severe outcomes such as hospitalizations and death, the logic is nonetheless tempting: if 62% fewer people get influenza, then would not one expect 62% fewer of all of influenza's complications? Not necessarily so. The reason is that the 62% reduction statistic almost certainly does not hold true for all subpopulations. In fact, there are good reasons to assume it does not. It is well known that influenza infections are more severe for certain groups of people, such as the frail older population, compared with others like healthy young adults. The CDC study did not present the statistics by age or health status, but an update of the study released one month later showed 90% of participants were younger than 65 years, and for older people, there was no significant benefit (vaccine effectiveness was 27%; 95% confidence interval, 31% to 59%).[10]

So how could these studies—both published in high impact, peer reviewed journals and carried out by academic and government researchers with non-commercial funding—get it wrong? Consider one study the CDC does not cite, which found influenza vaccination associated with a 51% reduced odds of death in patients hospitalized with pneumonia (28 of 352 [8%] vaccinated subjects died versus 53 deaths among 352 [15%] unvaccinated control subjects).[16] Although the results are similar to those of the studies CDC does cite, an unusual aspect of this study was that it focused on patients outside of the influenza season—when it is hard to imagine the vaccine could bring any benefit. And the authors, academics from Alberta, Canada, knew this: the purpose of the study was to demonstrate that the fantastic benefit they expected to and did find—and that others have found, such as the two studies that CDC cites—is simply implausible, and likely the product of the "healthy-user effect" (in this case, a propensity for healthier people to be more likely to get vaccinated than less healthy people). Others have gone on to demonstrate this bias to be present in other influenza vaccine studies.[17 18] Healthy user bias threatens to render the observational studies, on which officials' scientific case rests, not credible.

Yet for most people, and possibly most doctors, officials need only claim that vaccines save lives, and it is assumed there must be solid research behind it. But for those that bother to read the CDC's national guidelines[19]—a 68 page document of 33 360 words and 552 references—one finds that the evidence cited is these observational studies that the agency itself acknowledges may be undermined by bias. The guidelines state:

". . . studies demonstrating large reductions in hospitalizations and deaths among the vaccinated elderly have been conducted using medical record databases and have not measured reductions in laboratory-confirmed influenza illness. These studies have been challenged because of concerns that they have not controlled adequately for differences in the propensity for healthier persons to be more likely than less healthy persons to receive vaccination."[19]

CDC does not rebut or in any other way respond to these criticisms. It simply acknowledges them, and leaves it at that.

If the observational studies cannot be trusted, what evidence is there that influenza vaccines reduce deaths of older people—the reason the policy was originally created? Virtually none. Theoretically, a randomized trial might shine some light—or even settle the matter. But there has only been one randomized trial of influenza vaccines in older people—conducted two decades ago—and it showed no mortality benefit (the trial was not powered to detect decreases in mortality or any complications of influenza). This means that influenza vaccines are approved for use in older people despite any clinical trials demonstrating a reduction in serious outcomes. Approval is instead tied to a demonstrated ability of the vaccine to induce antibody production, without any evidence that those antibodies translate into reductions in illness.

Perhaps most perplexing is officials' lack of interest in the absence of good quality evidence. Anthony Fauci, director of the US National Institute of Allergy and Infectious Diseases, told the *Atlantic* that it "would be unethical" to do a placebo controlled study of influenza vaccine in older people.[20] The reason? Placebo recipients would be deprived of influenza vaccines—that is, the standard of care, thanks to CDC guidelines.

This is not to say influenza vaccines have no proven benefit. Many randomized controlled trials of influenza vaccines have been conducted in the healthy adult population, and a systematic review found that, depending on vaccine-virus strain match, vaccinating between 33 and 100 people resulted in one less case of influenza.[21] No evidence exists, however, to show that this reduction in risk of symptomatic influenza for a specific population—here, among healthy adults—extrapolates into any reduced risk of serious complications from influenza such as hospitalizations or death in another population (complications largely occur among the frail, older population). This fact seems hard for many health commentators to grasp, who seem all too

ready to take the largest statistic and apply it to all outcomes for all populations. At a press briefing this winter, CDC director Thomas Frieden said a preliminary CDC study had found "the overall vaccine effectiveness to be 62%," He explained that this estimate of relative risk reduction: "means that if you got vaccinated you're about 60% less likely to get the flu that requires you to go to your doctor." On the evening news, the CDC's message was translated into a claim that influenza vaccines will cut the risk of death by 62%, despite the fact that the CDC study did not even measure mortality (box 2). Reflecting on the same CDC study, two authors editorialized in the *Journal of the American Medical Association* that there exists an irrational pessimism about influenza vaccine: "A prevention measure that reduced the risk of a serious outcome by 60% in most instances would be a noted achievement; yet for influenza vaccine, it is seen as a 'failure.'" Here, too, the authors appear unaware that the CDC study they cite did not measure any "serious outcome" like pneumonia, only medically attended acute respiratory illness with influenza confirmed by the laboratory.

Officials say influenza vaccines are safe

The CDC's universal influenza vaccination recommendation carries the implicit message that, beyond those for whom the vaccine is contraindicated, influenza vaccine can only do good; there is no need to weigh risks against benefits. In October 2009, the US National Institutes of Health produced a promotional YouTube video featuring Fauci. Urging US citizens to get vaccinated against the H1N1 influenza, Fauci stressed the vaccine's safety: "the track record for serious adverse events is very good. It's very, very, very rare that you ever see anything that's associated with the vaccine that's a serious event."

Months later, Australia suspended its influenza vaccination program in under five year olds after many (one in every 110 vaccinated) children had febrile convulsions after vaccination. Another serious reaction to influenza vaccines—and also unexpected—occurred in Sweden and Finland, where H1N1 influenza vaccines were associated with a spike in cases of narcolepsy among adolescents (about one in every 55 000 vaccinated). Subsequent investigations by governmental and non-governmental researchers confirmed the vaccine's role in these serious events.[22-25]

Selling sickness: what's in a name?

Drug companies have long known that to sell some products, you would have to first sell people on the disease. Early 20th century advertising for the mouthwash Listerine, for example, warned readers of the problem of "halitosis"—thereby turning bad breath into a widespread social concern.[26] Similarly, in the 1950s and 1960s, Merck launched an extensive campaign to lower the diagnostic threshold for hypertension, and in doing so enlarging the market for its diuretic drug, Diuril (chlorothiazide).[27] Today drug companies suggest that we have underdiagnosed epidemics of erectile dysfunction, social anxiety disorder, and female sexual dysfunction, each with their own convenient acronym and an approved medication at the ready. Could influenza—a disease known for centuries, well defined in terms of its etiology, diagnosis, and prognosis—be yet one more case of disease mongering? I think it is. But unlike most stories of selling sickness, here the salesmen are public health officials, worried little about which brand of vaccine you get so long as they can convince you to take influenza seriously.

Marketing influenza vaccines thus involves marketing influenza as a threat of great proportions. The CDC's website explains that "Flu seasons are unpredictable and can be severe," citing a death toll of "3000 to a high of about 49 000 people." However, a far less volatile and more reassuring picture of influenza seems likely if one considers that recorded deaths from influenza declined sharply over the middle of the 20th century, at least in the United States, all before the great expansion of vaccination campaigns in the 2000s, and despite three so-called "pandemics" (1957, 1968, 2009) (fig 1).⇓

But perhaps the cleverest aspect of the influenza marketing strategy surrounds the claim that "flu" and "influenza" are the same. The distinction seems subtle, and purely semantic. But general lack of awareness of the difference might be the primary reason few people realize that even the ideal influenza vaccine, matched perfectly to circulating strains of wild influenza and capable of stopping all influenza viruses, can only deal with a small part of the "flu" problem because most "flu" appears to have nothing to do with influenza. Every year, hundreds of thousands of respiratory specimens are tested across the US. Of those tested, on average 16% are found to be influenza positive. (fig 2).⇓

All influenza is "flu," but only one in six "flus" might be influenza. It's no wonder so many people feel that "flu shots" don't work: for most flus, they can't.

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Table

Table 1| **Table 1. Expansion of influenza vaccination recommendations, 1960 to present**

Population	1960	1984	1987	2000	2004	2006	2008	2009	2010
Recommendations by age									
Adults ≥ 65 years	X	X	X	X	X	X	X	X	X
Adults ≥ 50 years				X	X	X	X	X	X
Children 6 to 23 months					X	X	X	X	X
Children 6 to 59 months						X	X	X	X
Children 6 months to 18 years, if feasible							X	X	X
Children 6 months to 18 years								X	X
Everyone ≥ 6 months									X
Recommendations by condition or occupation									
Pregnant women (2nd and 3rd trimester)				X	X	X	X	X	X
Pregnant women (all trimesters)					X	X	X	X	X
Healthcare workers		X	X	X	X	X	X	X	X
Household contacts of high risk groups			X	X	X	X	X	X	X
Household contacts and out of home caregivers of children 0-23 months					X	X	X	X	X
Household contacts and out of home caregivers of children 0-59 months						X	X	X	X

Sources: Advisory Committee on Immunization Practices,[5, 44-48] Osterholm,[49] and Layton et al.[50]

Figures

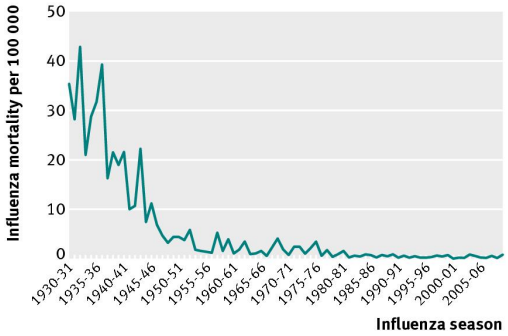

Fig 1 Crude mortality per 100 000 population, by influenza season (July to June of the following year), for seasons 1930-31 to 2009-10, US. Data sources: Doshi P. *Am J Pub Health* 2008;98:939-45.

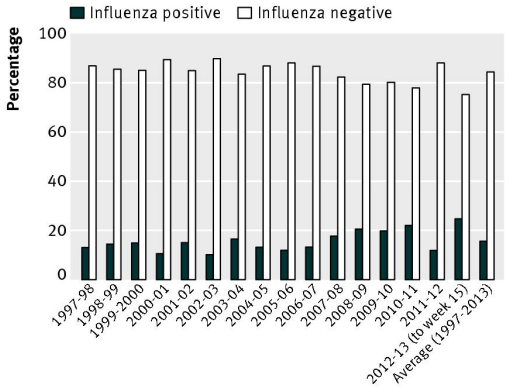

Fig 2 Proportion of specimens testing positive for influenza at World Health Organization (WHO) Collaborating Laboratories and National Respiratory and Enteric Virus Surveillance System (NREVSS) laboratories through the United States. Data are compiled and published by CDC.[28-43]