Twitter Thread by Jonathan Witt

Jonathan Witt
@Jonathan_Witt

Definitely not the first to post on this but am completely floored by a 2008 paper published in the Journal of Infectious Diseases by Professor David Morens (Medical Epidemiologist), Dr Jeffery Taubenberger (Virologist), and Dr Anthony Fauci (Immunologist) at the NIAID. 1/11

Predominant Role of Bacterial Pneumonia as a Cause of Death in Pandemic Influenza: Implications for Pandemic Influenza Preparedness

David M. Morens, Jeffery K. Taubenberger, and Anthony S. Fauci
National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

In the paper the authors question the cause of mortality during the 1918 pandemic and those which follow. They go on to hypothesize and prove that bacterial pneumonia is actually the prominent causative factor during viral respiratory pandemics. 2/11

An important question related to pandemic preparedness remains unanswered: what killed people during the 1918–1919 pandemic and subsequent influenza pandemics? In the present study, we have examined recut tissue specimens obtained during autopsy from 58 influenza victims in 1918–1919, and have reviewed epidemiologic, pathologic, and microbiologic data from published reports for 8398 postmortem examinations bearing on this question. We have also reviewed relevant information, accumulated over 9 decades, related to the circulation of descendants of the 1918 virus. With the recent reconstruction of the 1918 pandemic influenza virus, investigators have begun to examine why it was so highly fatal [6, 7]. Based on contemporary and modern evidence, we conclude here that influenza A virus infec-

Part of the methodology was examining several histological specimens which had been preserved from the pandemic. They found that in essentially every single case there was evidence of severe acute bacterial pneumonia either as predominant or in conjunction with virus. 3/11

Histologic examination of lung tissue from 1918 victims. The examination of recut lung tissue sections from 1918–1919 influenza case material revealed, in virtually all cases, compelling histologic evidence of severe acute bacterial pneumonia, either as the predominant pathology or in conjunction with underlying pathologic features now believed to be associated with influenza virus infection [10, 24] (figure

The paper notes that previous post mortem cultures picked up bacterial colonization with more than half of those being pathognomonic. 4/11

Bacteriologic studies in autopsy series during the 1918–1919 influenza pandemic. Negative lung culture results were uncommon in the 96 identified military and civilian autopsy series, which examined 5266 subjects (4.2% of results overall) (table 1; full bibliographic list available at http://www3.niaid.nih.gov/topics/Flu/1918/bibliography.htm). In the 68 higher-quality autopsy series, in which the possibility of unreported negative cultures could be excluded, 92.7% of autopsy lung cultures were positive for ⩾1 bacterium (table 1). Of these 96 series, 82 reported pneumopathogens in ⩾50% of lungs examined, either alone or in mixed culture results that included other bacteria (table 1). Outbreaks of meningococcal pneumo-

Morens et al. note that subsequent pandemic deaths were also attributable to secondary bacterial pneumonia following primary viral infection despite significant advancements in medicine. 5/11

Pathologic and bacteriologic information obtained from later pandemic and seasonal influenza cases. The viruses that caused the 1957 and 1968 pandemics were descendants of the 1918 virus in which 3 (the 1957 virus) or 2 (the 1968 virus) new avian gene segments had been acquired by reassortment [21]. Although lower pathogenicity resulted in far fewer deaths, hence fewer autopsies, most 1957–1958 deaths were attributable to secondary bacterial pneumonia, as had been the case in 1918. *Staphylococcus aureus*, a

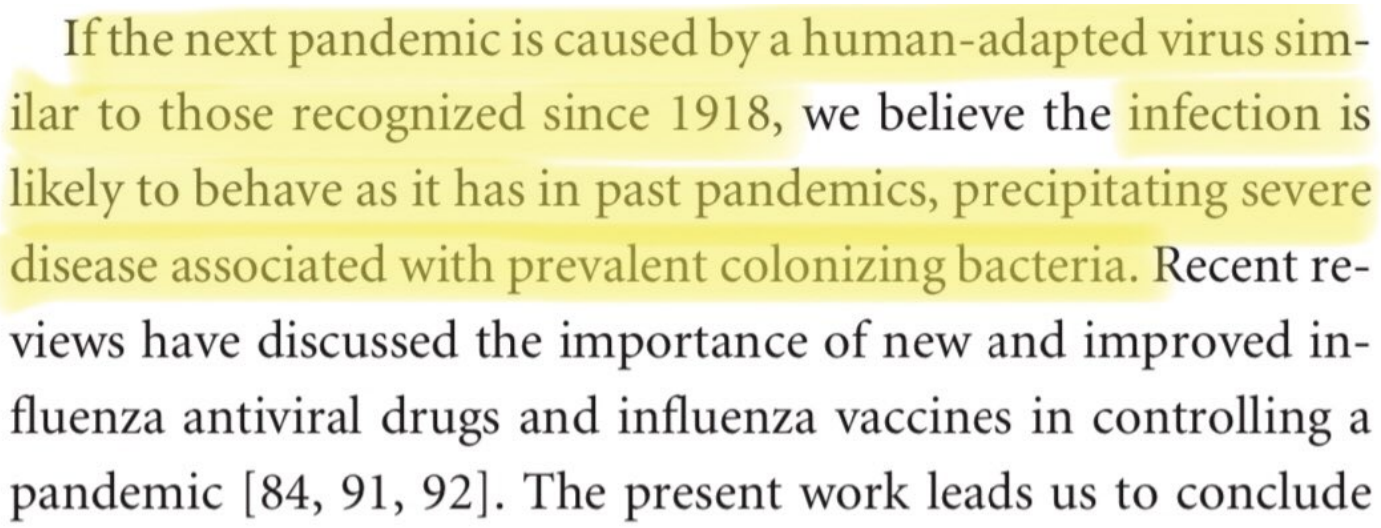
The paper concludes that ample evidence from influenza pandemics (and similar viruses) spanning almost a century indicates that viral deaths are actually due to bacterial infection. 6/11

We believe that the weight of 90 years of evidence (table 3), including the exceptional but largely forgotten work of an earlier generation of pathologists, indicates that the vast majority of pulmonary deaths from pandemic influenza viruses have resulted from poorly understood interactions between the infecting virus and secondary infections due to bacteria that colonize the upper respiratory tract. The data are consistent with a natural

The authors even provide a solid explanation for why we might be masking bacterial pneumonia deaths in this context, and note that primary viral pneumonia deaths are exceptionally rare “even in pandemic peaks”. 7/11

In the modern era, the widespread use of antibiotics and the establishment of life-prolonging intensive care unit treatment make it more difficult than it was in 1918 to document the importance of bacterial lung infection for influenza-related mortality. Influenza-associated pneumonia patterns may now be influenced by the administration of pneumococcus, *Hemophilus influenzae b,* and meningococcus vaccine, and cases have tended to occur in elderly individuals, who rarely undergo autopsy. The 1968 influenza pandemic was mild, and autopsy studies were uncommon [21]. Fatal cases of influenza-associated viral pneumonia that are considered to be “primary” (i.e., with little or no bacterial growth) continue to be identified [82, 83]; however, their incidence appears to be low, even in pandemic peaks. The

There’s then this throw forward to the “next pandemic” in which the authors note that a human-adapted virus (Influenza; SARS-CoV-2) will cause severe disease by bacterial colonization in the background of viral infection. 8/11


If the next pandemic is caused by a human-adapted virus similar to those recognized since 1918, we believe the infection is likely to behave as it has in past pandemics, precipitating severe disease associated with prevalent colonizing bacteria. Recent reviews have discussed the importance of new and improved influenza antiviral drugs and influenza vaccines in controlling a pandemic [84, 91, 92]. The present work leads us to conclude

The paper was published in 2008 by 3 leading scientists at least one of whom now seems to have forgotten he ever wrote this. It's available for viewing and download here:

https://t.co/urpWqLFpij

9/11

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David M. Morens, Jeffery K. Taubenberger, and Anthony S. Fauci

National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

(See the editorial commentary by McCullers, on pages XXX–XXX.)

Background. Despite the availability of published data on 4 pandemics that have occurred over the past 120 years, there is little modern information on the causes of death associated with influenza pandemics.

Methods. We examined relevant information from the most recent influenza pandemic that occurred during the era prior to the use of antibiotics, the 1918–1919 "Spanish flu" pandemic. We examined lung tissue sections obtained during 58 autopsies and reviewed pathologic and bacteriologic data from 109 published autopsy series that described 8398 individual autopsy investigations.

Results. The postmortem samples we examined from people who died of influenza during 1918–1919 uniformly exhibited severe changes indicative of bacterial pneumonia. Bacteriologic and histopathologic results from published autopsy series clearly and consistently implicated secondary bacterial pneumonia caused by common upper respiratory–tract bacteria in most influenza fatalities.

Conclusions. The majority of deaths in the 1918–1919 influenza pandemic likely resulted directly from secondary bacterial pneumonia caused by common upper respiratory–tract bacteria. Less substantial data from the subsequent 1957 and 1968 pandemics are consistent with these findings. If severe pandemic influenza is largely a problem of viral-bacterial copathogenesis, pandemic planning needs to go beyond addressing the viral cause alone (e.g., influenza vaccines and antiviral drugs). Prevention, diagnosis, prophylaxis, and treatment of secondary bacterial pneumonia, as well as stockpiling of antibiotics and bacterial vaccines, should also be high priorities for pandemic planning.

"If grippe condemns, the secondary infections execute" [1, p. 448].

——Louis Cruveilhier, 1919

Influenza pandemic preparedness strategies in the United States [2] assume 3 levels of potential severity corresponding to the 20th century pandemics of H1N1 "Spanish flu" (1918–1919), H2N2 "Asian flu" (1957–1958), and H3N2 "Hong Kong flu" (1968–1969), which were responsible for an estimated 675,000 [3], 86,000 [4], and 56,300 [5] excess deaths in the United States, respectively. Extrapolation from 1918–1919 pandemic data to the current population and age profile has led United States government officials to plan for more than 1.9 million excess deaths during a severe pandemic [2].

An important question related to pandemic preparedness remains unanswered: what killed people during the 1918–1919 pandemic and subsequent influenza pandemics? In the present study, we have examined recut tissue specimens obtained during autopsy from 58 influenza victims in 1918–1919, and have reviewed epidemiologic, pathologic, and microbiologic data from published reports for 8398 postmortem examinations bearing on this question. We have also reviewed relevant information, accumulated over 9 decades, related to the circulation of descendants of the 1918 virus. With the recent reconstruction of the 1918 pandemic influenza virus, investigators have begun to examine why it was so highly fatal [6, 7]. Based on contemporary and modern evidence, we conclude here that influenza A virus infec-

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Reprints or correspondence: David M. Morens, MD, Bldg. 31, Room 7A-10, 31 Center Dr., MSC 2520, National Institute of Allergy and Inectious Diseases, National Institutes of Health, Bethesda, MD 20892–2520 (dmorens@niaid.nih.gov).

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If we knew in 2008 that co-infection during respiratory pandemics is the major driver of mortality, then why are we basically ignoring this entirely in 2020?

New variant and less than perfect vaccine, or bacterial infection we're not treating properly for viral obsession? 10/11

There are so many questions to be asked given the existence of this paper and the people who published it. We are treating pandemic science as if it started in March of this year when in fact we have lots of good data prior to this - if only we'd read it. 11/11