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I am involved in research grants and funding from industry	Unrelated to this presentation: Pfizer (epidemiological study on *N.meningitidis*), terminated	NA
I am currently participating in or have participated in a clinical trial within the past two years	Unrelated to this presentation: Sanofi Pasteur (*C.difficile* vaccine RCT), terminated	NA
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Burden of influenza: how the big picture is estimated?

Numerous heterogeneous sources of data, most without laboratory confirmation
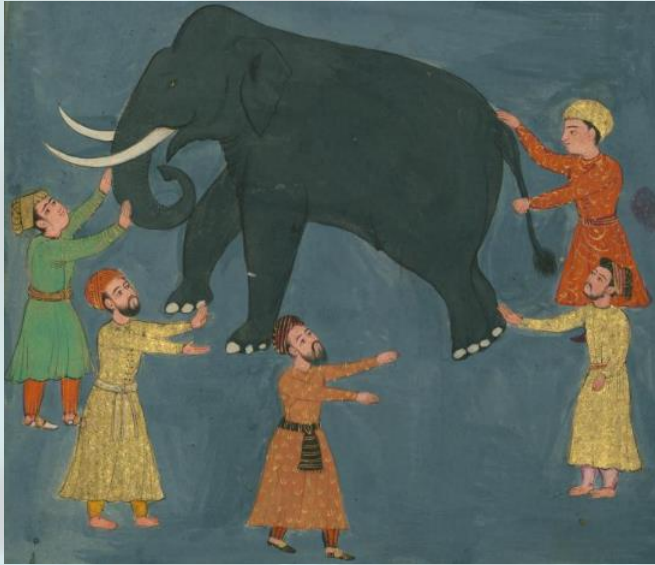
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2 main methods

- Statistical (indirect) methods applied to administrative data

    The Need for Validation of Statistical Methods for Estimating Respiratory Virus–Attributable Hospitalization

    Rodica Gilca, Gaston De Serres, Danuta Skowronski, Guy Boivin, and David L. Buckeridge   *Am J Epidemiol*   2009
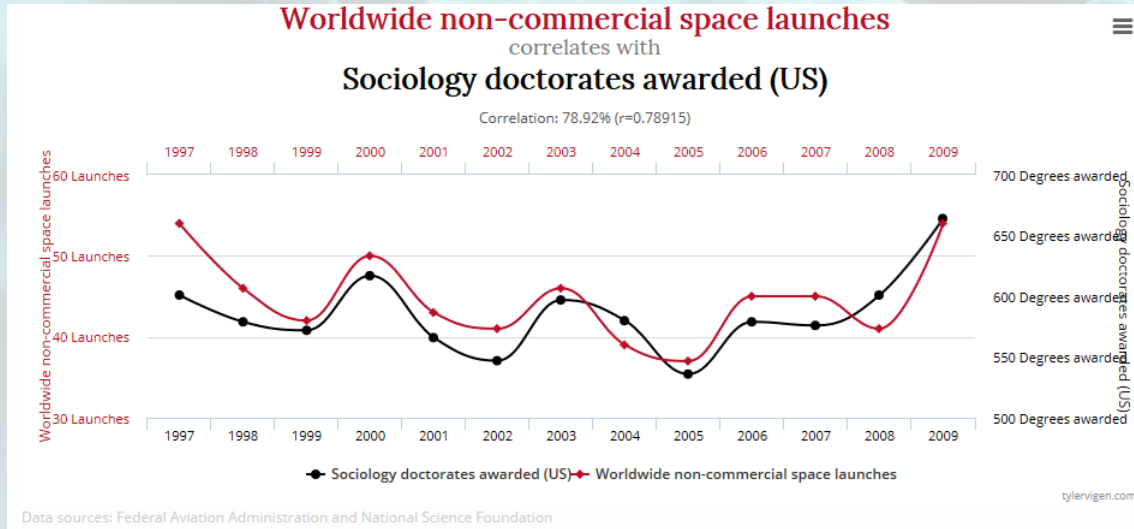
- Population-based surveillance data with direct prospective laboratory confirmation

How statistical models measure association with influenza?
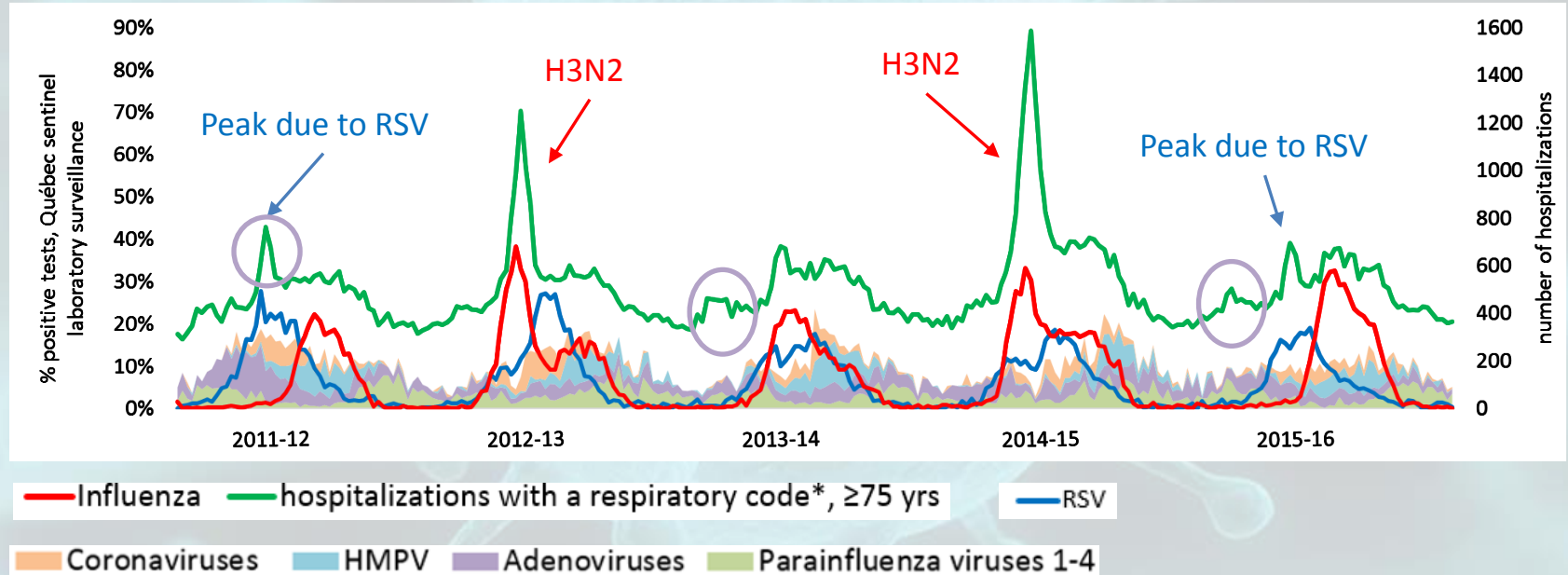
*Respiratory code: ICD-10 codes J00 – J990 in the provincial hospitalization database

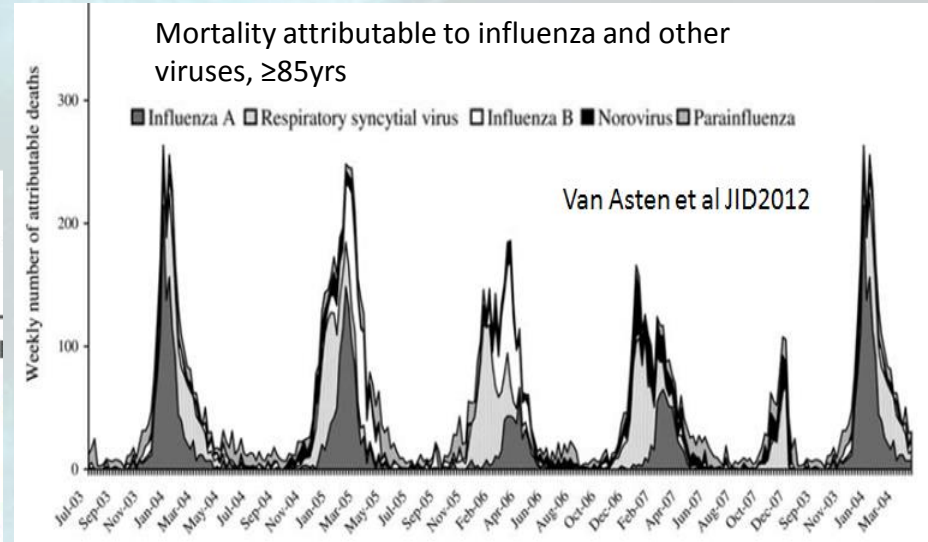# A perfectly adjusted model does not necessarily reflect causality

The role of other factors may be detected only by including them into the model, and if robust source data are available

Predictors of hospitalization for lower respiratory tract infection in children aged <2 years in the province of Quebec, Canada

Z. ZHOU[1], R. GILCA[2], G. DECEUNINCK[1], F. D. BOUCHER[3], H. CHAREST[4] AND P. DE WALS[5]

Epidemiol. Infect. 2015

Predictors	Additive model*	
	%	(95% CI)
Viral circulation‡	Fraction of admissions for LRTI	
Respiratory syncytial virus	27·5	(23·6 to 31·4)
Human metapneumovirus	3·8	(2·1 to 5·5)
Influenza	1·4	(−0·4 to 3·1)
Temperature (°C)§	37·1	(30·1 to 43·3)

Mortality attributable to influenza and other viruses, ≥85yrs

□ Influenza A □ Respiratory syncytial virus □ Influenza B ■ Norovirus □ Parainfluenza

Van Asten et al JID2012

Québec prospective study

- 4 acute care community hospitals ; ≈10% Québec population

- **Peaks*** of influenza seasons (≥15% influenza-positive specimens from Quebec sentinel laboratories)

- All patients hospitalized with fever/respiratory symptoms systematically tested by multiplex PCR for 16 respiratory viruses
  - 60-80% of enrolled patients present with standard ILI definition (CDC/PHAC)
  - Includes pneumonia, sepsis, COPD, cardiological Dx
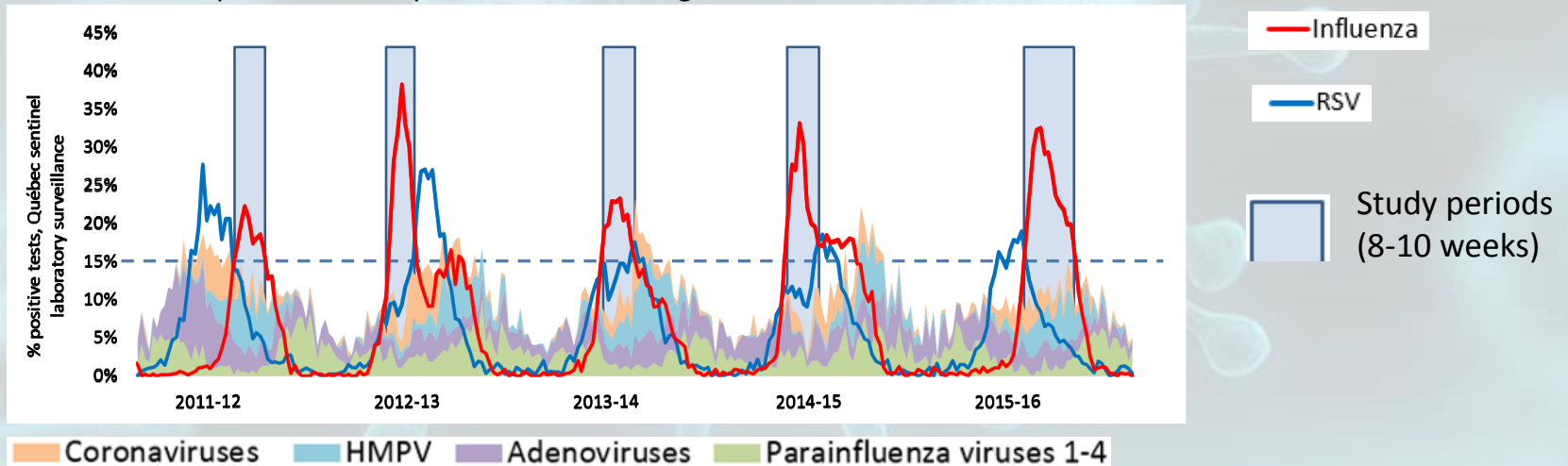
Québec prospective study:

Proportions of influenza and other respiratory viruses in patients hospitalized with fever/respiratory symptoms during the peaks* of 5 influenza seasons

0-17 yrs | **18-64 yrs** | **65-74 yrs** | **≥75 yrs**

Legend:
- ■ Influenza
- ■ Other virus
- ■ No virus
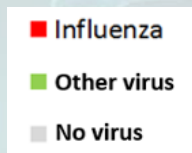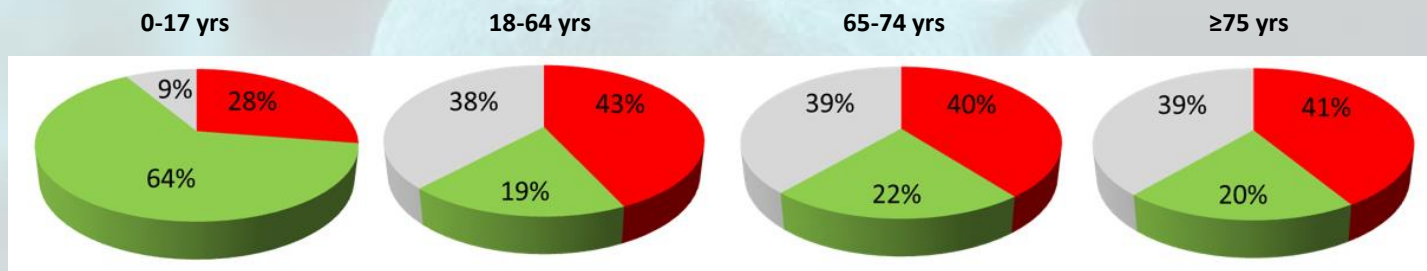
- Influenza includes coinfections with other viruses (8% overall, up to >50% in children)

Other viruses:
- Respiratory syncytial virus 48%
- Entero/rhinoviruses 19%
- Metapneumovirus 12%
- Coronaviruses 11%
- Parainfluenza viruses 8%
- Adenovirus 2%
- Bocavirus 1%

*Peak= 8-10 weeks of intense influenza circulation

Influenza-associated hospitalizations* in Québec

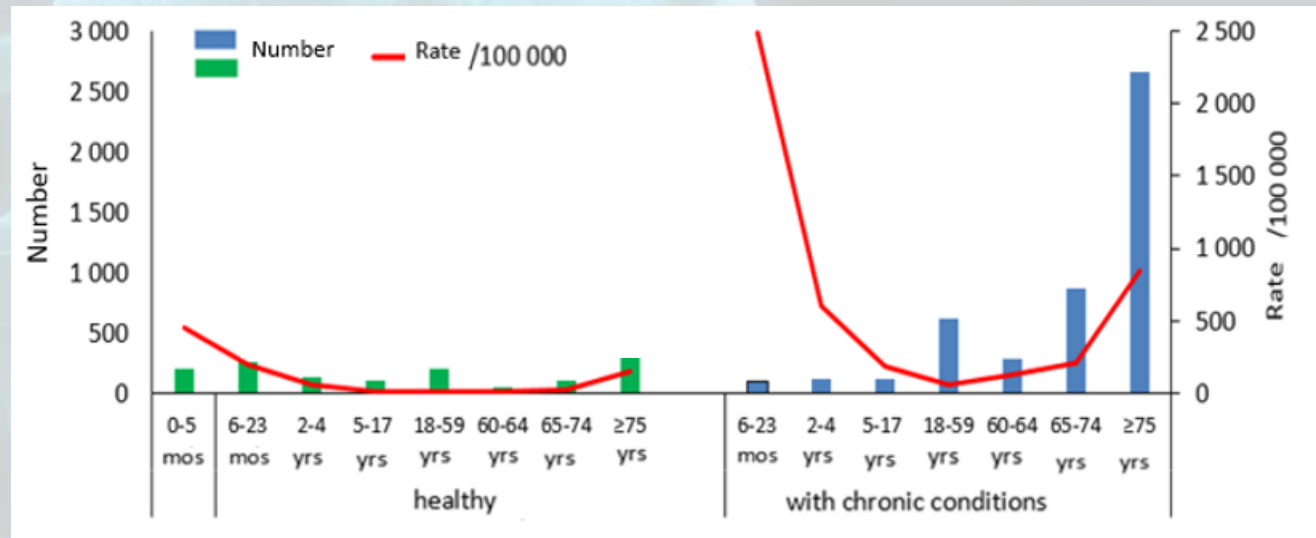**Yearly (5 seasons) average for Québec, overall: ≈6,200 (76/100,000)**

Among the highest in the literature

Chronic conditions:
rate 12-fold higher than in healthy

Healthy children:
Short length of stay
(median 3 vs 6 days in 75+)

*Québec prospective study data extrapolated to entire Québec population for adults and healthy children, IMPACT data extrapolated to entire Québec for children with chronic conditions

Proportion of deaths among patients hospitalized with a confirmed respiratory virus infection
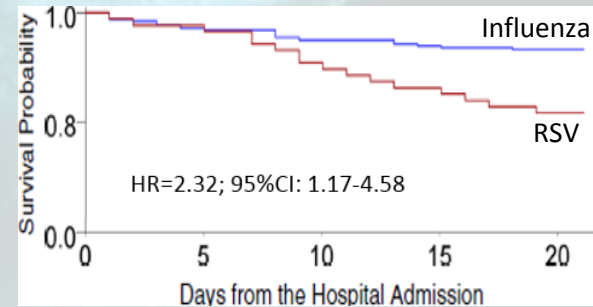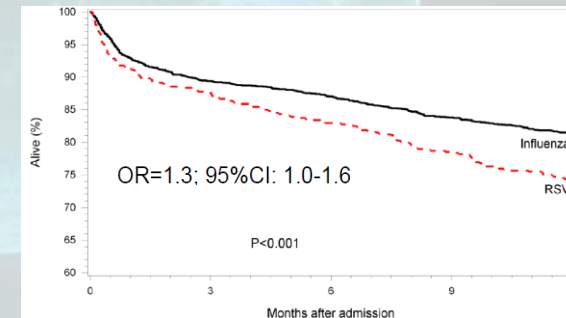
Québec prospective study
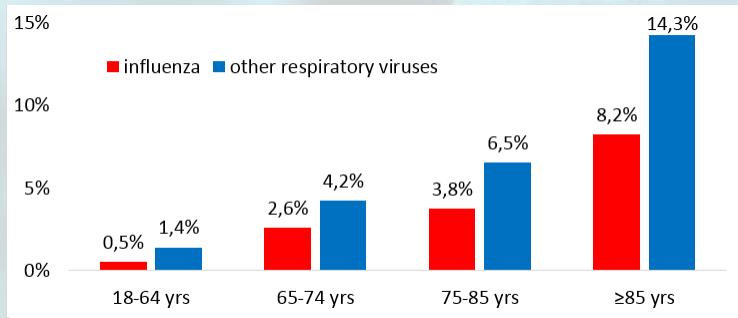
No death recorded in <18 yrs in the prospective study

For children, rates reported in the literature used, usually obtained during severe influenza seasons

Greater mortality in adults hospitalized with RSV than in those with influenza

≥18 years, South Korea

Kwon et al, BMC Infectious Diseases 2017

≥60 years, Kaiser Permanente

Ackerson et al, CID 2018

Influenza-associated deaths* in Québec

Yearly (5 seasons) average, including deaths outside acute-care hospitals: 417(5.2/100,000)

Chronic conditions:
rate >20-fold higher than in healthy

LTCF residents:
- 50% of all influenza deaths

Our results are similar to recent published estimates

Estimates of global seasonal influenza-associated respiratory mortality: a modelling study *Lancet 2018; 391: 1285–300*

Global Seasonal Influenza-associated Mortality Collaborator Network* **Funding None.**

Influenza is **not the main or contributing cause of death** in >1/3 of the deaths with confirmed influenza in elderly
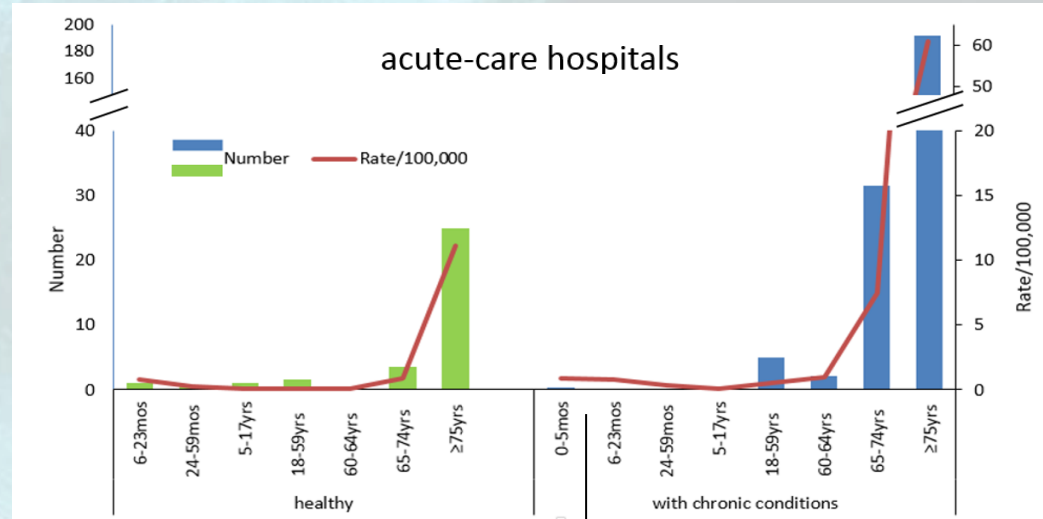
*Estimates based on Québec prospective study; declarations of outbreaks in LTCF (long-term care facilities), administrative hospitalization and death databases, IMPACT and literature data for children

Summary

- Published estimates of burden attributable to influenza are highly variable and dependent on the methods used

- If patients are not tested for respiratory viruses, what is due to other viruses or other factors is often attributed to influenza, especially by indirect methods
  – Burden due to other respiratory viruses is at least as important as the burden of influenza

- Burden of influenza is considerably more important in persons with chronic conditions compared to healthy persons (up to 100-fold difference)

- The great majority of deaths (90%) occur in ≥75yrs and in persons with chronic conditions; 50% in LTCF residents
  – An important proportion of influenza-confirmed deaths (>1/3) is not due to influenza

Conclusion

- The vaccine can prevent only what is preventable

Let us open the eyes!

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Acknowledgments

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- Ministry of Health of Québec

- IMPACT network