The Spanish flu in Denmark 1918: three contrasting approaches

Niels Keiding
Department of Biostatistics
University of Copenhagen

DIMACS/ECDC Workshop:
Spatio-temporal and Network Modeling of Diseases III
on the occasion of Professor Klaus Dietz’ retirement

Tübingen 24 October 2008

The Spanish flu in Denmark 1918 as seen 90 years later

- Descriptive presentation of incidence and mortality in (all of) Denmark

  I.V. Kolte, P. Skinhøj, N. Keiding, E. Lynge (2008). The Spanish flu in Denmark. *Scand.J.Infect.Dis*. **40**, 538-546

- Analytic study of incidence, hospitalization and mortality in Copenhagen

  V. Andreasen, C. Viboud, L. Simonsen (2008). Epidemiologic characterization of the 1918 influenza pandemic summer wave in Copenhagen: Implication for pandemic control strategies. *J.Inf.Dis*. **197**, 270-278

- The demographic approach: Cause-deleted survival

  V.Canudas-Romo, A.Erlangsen (2008). Denmark: The lowest excess mortality during influenza pandemic of 1918. Presented at Population Association of America meeting, New Orleans

Descriptive presentation of incidence and mortality in all of Denmark

I.V. Kolte, P. Skinhøj, N. Keiding, E. Lynge (2008). The Spanish flu in Denmark.
Scand.J.Infect.Dis. **40**, 538-546.

Sources: influenza *incidence* data from yearly “Medicinalindberetning”, based on reports from local doctors to county health officers, printed by National Board of Health. Sex/age groups:

<table>
<tr><th>age</th><th>0-1</th><th>1-4</th><th>5-14</th><th>15-64</th><th>65-</th></tr>
<tr><td>male</td><td rowspan="2"></td><td rowspan="2"></td><td rowspan="2"></td><td></td><td></td></tr>
<tr><td>female</td><td></td><td></td></tr>
</table>

Sources, cont.

Mortality data: Total rural area: yearly total no. of deaths, not age-stratified. Cause of death not required in rural areas until 1920.

Each town: *yearly* total no. of deaths, not age-stratified

Monthly data for total numbers in towns stratified:

1. Copenhagen (capital)
2. Frederiksberg (capital)
3. Provincial towns on islands
4. Towns in Jylland

For each sex, age groups

1m 2-3m 4-12m, 2y, 3, 4, 5-9, 10-14, 15-19, 20-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75-84, 85-y.

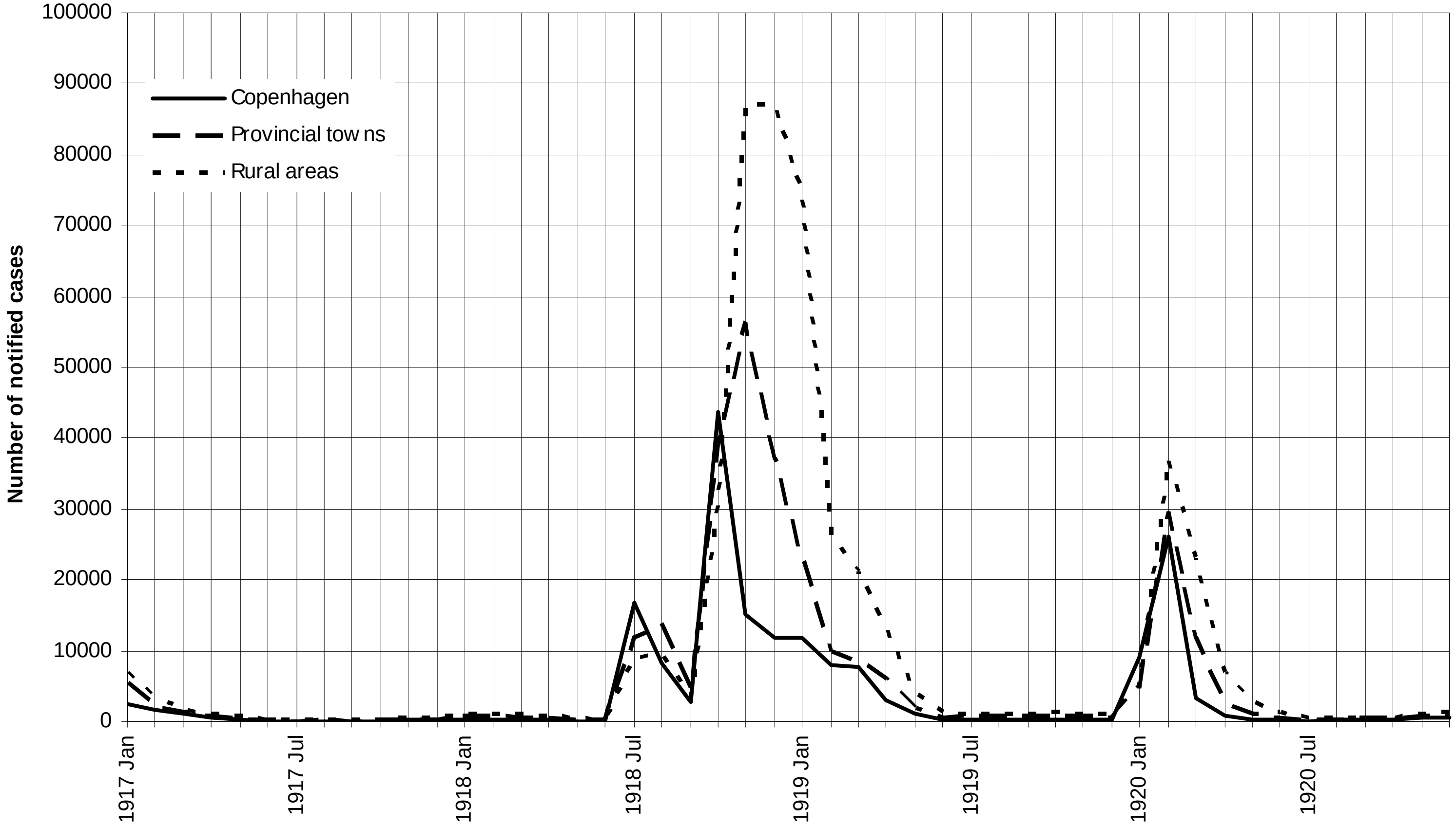
Total mortality and main cause of death. We use *alii morbi epidemici* = “other infectious diseases” which was dominated by influenza in those years.

Sources, cont.

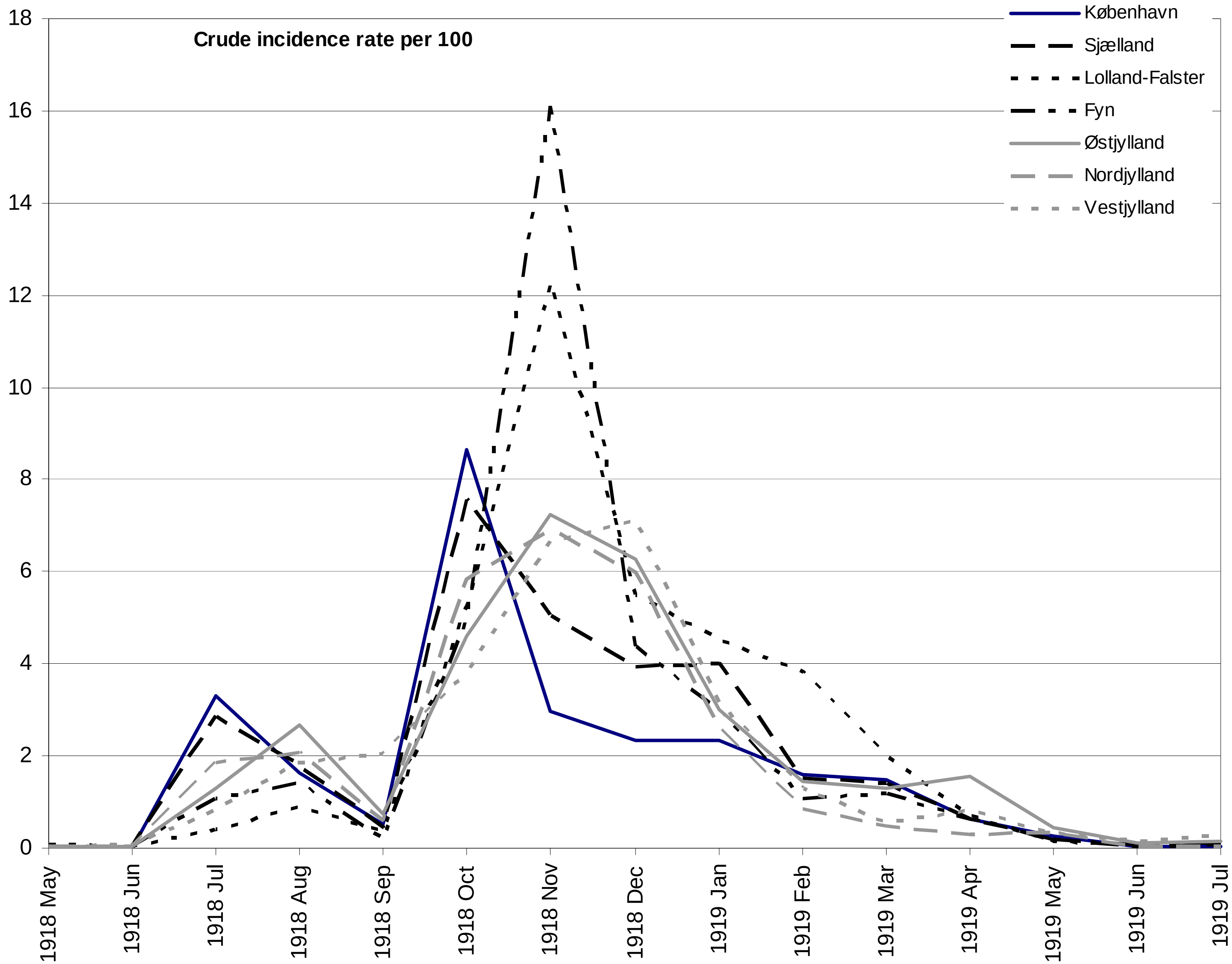
Census 1916: published only by geographical area, no age/sex stratification

Census 1921: geographical area, sex, 1-year age groups.

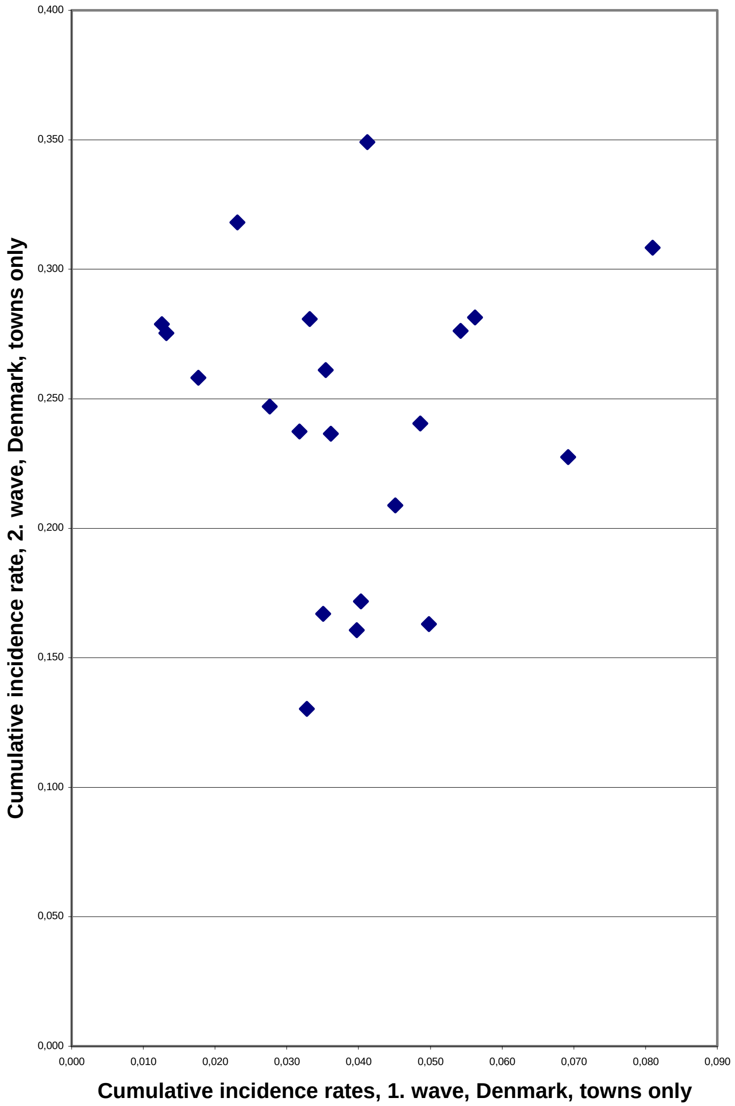

1. Copenhagen
2. County of Copenhagen
3. Roskilde
4. Frederiksberg
5. Holbæk
6. Sorø
7. Præstø
8. Lolland-Falster
9. Bornholm
10. Svendborg
11. Odense
12. Assens
13. Vejle
14. Skanderborg
15. Aarhus
16. Randers
17. Aalborg
18. Hjørring
19. Thisted
20. Viborg
21. Ringkøbing
22. Ribe
German territory until 1920

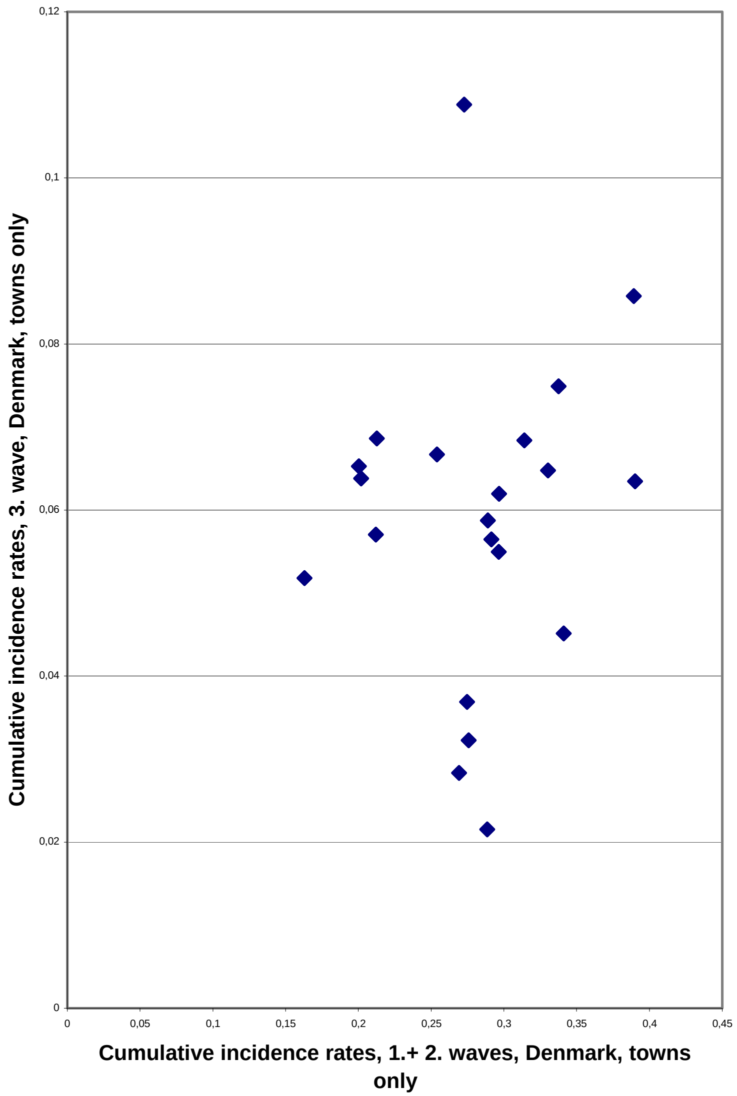


Number of notified cases
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
Copenhagen
Provincial tow ns
Rural areas
1917 Jan
1917 Jul
1918 Jan
1918 Jul
1919 Jan
1919 Jul
1920 Jan
1920 Jul

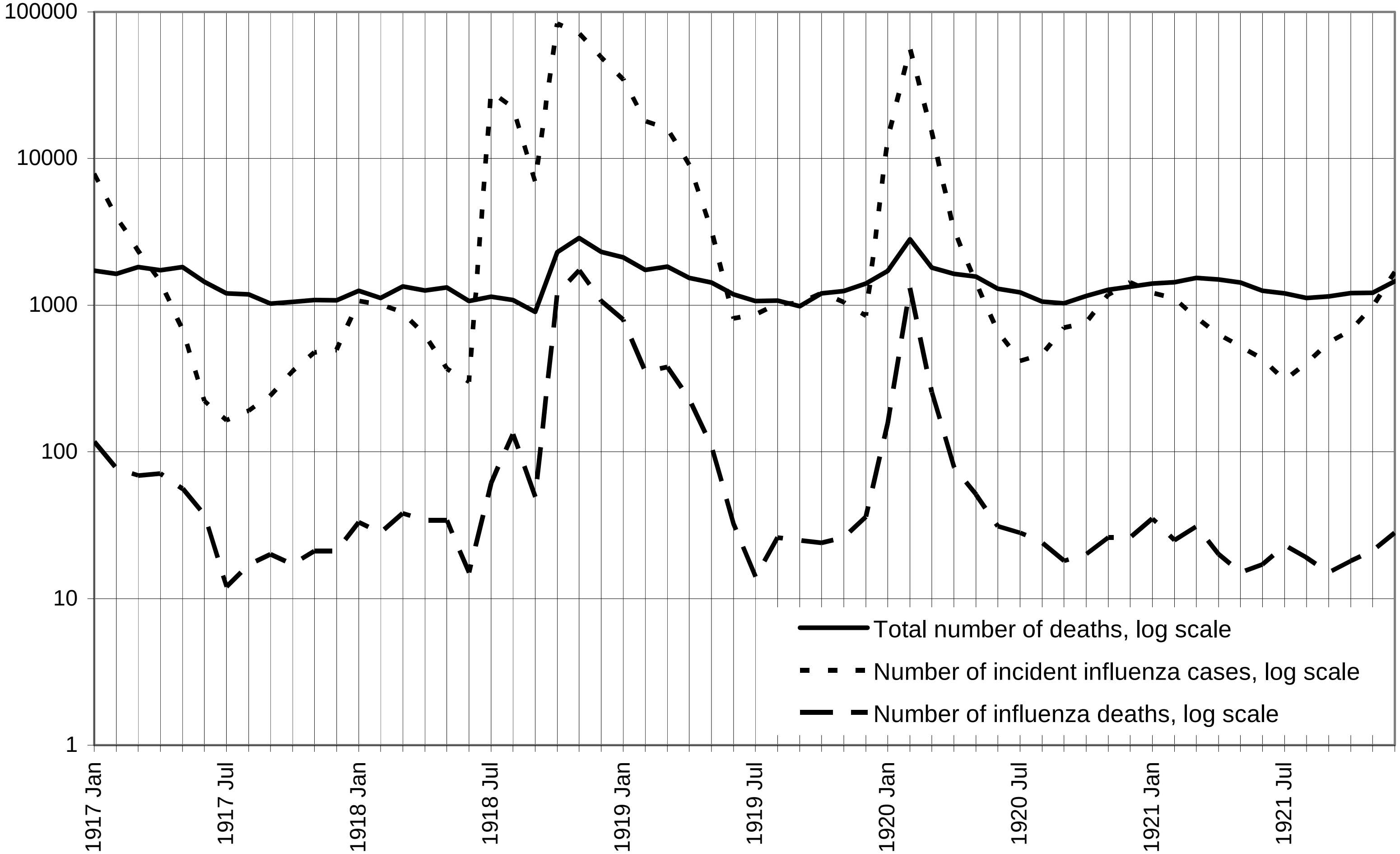

Crude incidence rate per 100
København
Sjælland
Lolland-Falster
Fyn
Østjylland
Nordjylland
Vestjylland
0
2
4
6
8
10
12
14
16
18
1918 May
1918 Jun
1918 Jul
1918 Aug
1918 Sep
1918 Oct
1918 Nov
1918 Dec
1919 Jan
1919 Feb
1919 Mar
1919 Apr
1919 May
1919 Jun
1919 Jul

Towns only

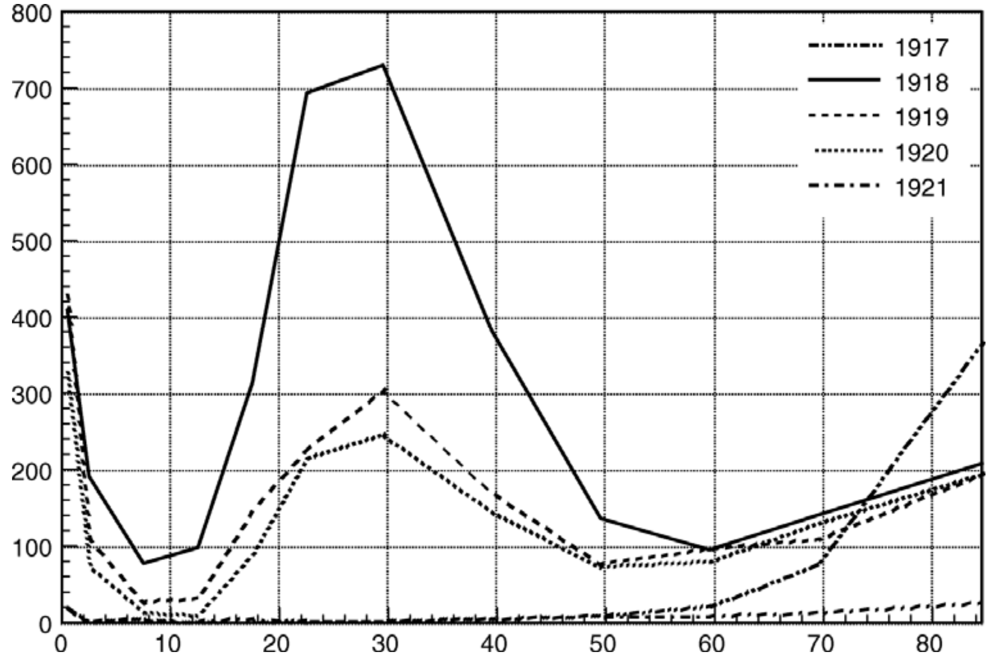




Correlation between waves: very small



Note the very moderate variation in total mortality



The W-shaped age-specific *alii morbi epidemici* death rate in Denmark 1917-1921. Towns only.

Some notable features from descriptive data

Delay capital → urban → rural

Clear initial peak in summer 1918.

But hard to identify town-specific correlation between waves.

Is the serious epidemic in summer 1920 a third wave of the Spanish flu?

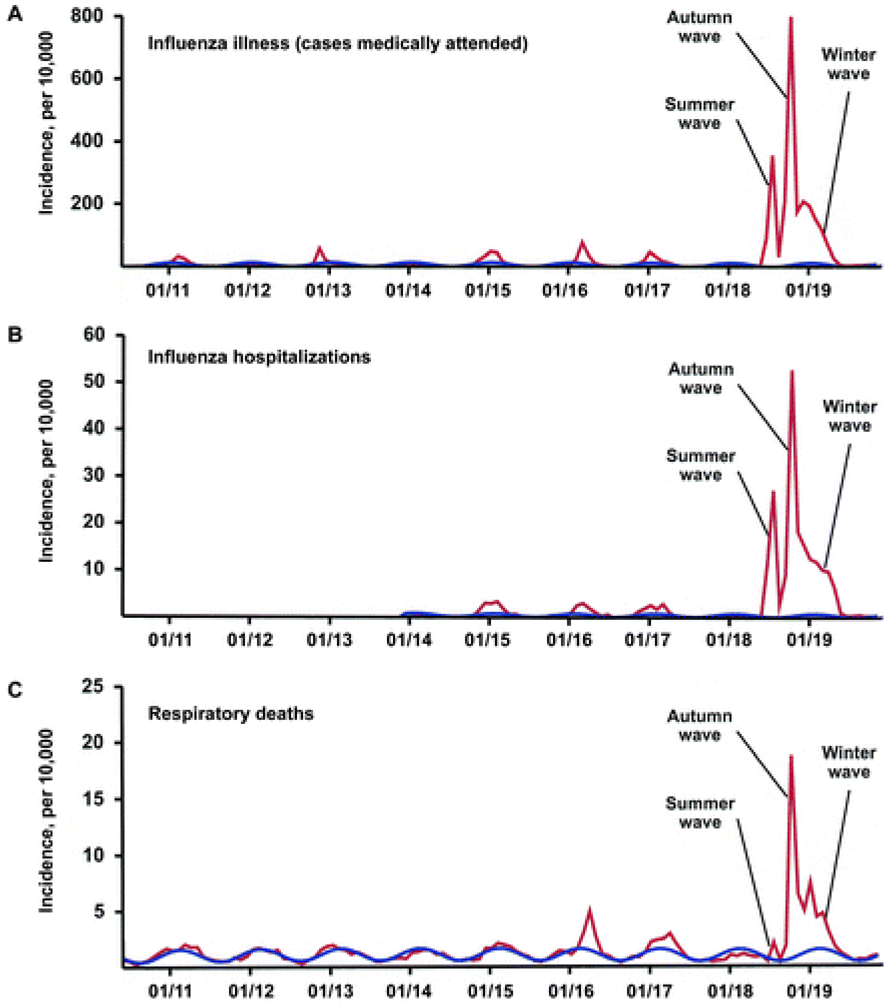
Analytic study of incidence, hospitalization and mortality in Copenhagen

V. Andreasen, C. Viboud, L. Simonsen (2008).
Epidemiologic characterization of the 1918 influenza pandemic summer wave in Copenhagen: implication for pandemic control strategies. *J.Inf.Dis.* **197**, 270-278.

Sources: Epidemiological surveillance system for infectious diseases in Copenhagen containing **weekly**

- reports from general practitioners on new cases (by cause)
- reports on hospitalisations (by cause)
- reports on deaths (by cause and age)

Excess morbidity and mortality calculated using Serfling et al. (1967) seasonal regression models to establish “baseline” levels in the absence of influenza.



Blue lines: Serfling base line

Estimation of R and R_0 from incidence data

Assume that in the initial (exponentially growing) phase of the epidemic the weekly number of influenza-like-illnesses (ILI) is Poisson-distributed with mean $\lambda_i = \alpha\gamma^i$, $i = 1, \cdots, T$ weeks.

Assess pragmatically the start and the end of the exponential growth period $[0, T]$. Mostly $T = 3$, surprisingly short. (Usual explanation in terms of depletion of susceptible unrealistic. Most likely alternative explanation: behavioural change).This yields a maximum likelihood estimate of γ with standard error estimates.

From weekly growth factor γ to reproduction numbers R, R_0

Define $J(t) = \left(J_1(t), \cdots, J_8(t)\right)^T$

where $J_i(t) = \#$ hosts at time t infected at day $t-i$

and v_i = relative infectivity at day i after being infected.

Then

$$J(t+1) = \begin{pmatrix} Rv_1 & Rv_2 & \cdots & Rv_7 & Rv_8 \\ 1 & 0 & \cdots & 0 & 0 \\ 0 & 1 & \cdots & 0 & 0 \\ \vdots & \vdots & & & \\ 0 & 0 & \cdots & 1 & 0 \end{pmatrix} J(t)$$

Mean generation time used to be assumed to be 4 days, now sometimes assumed to be 2.6 days.

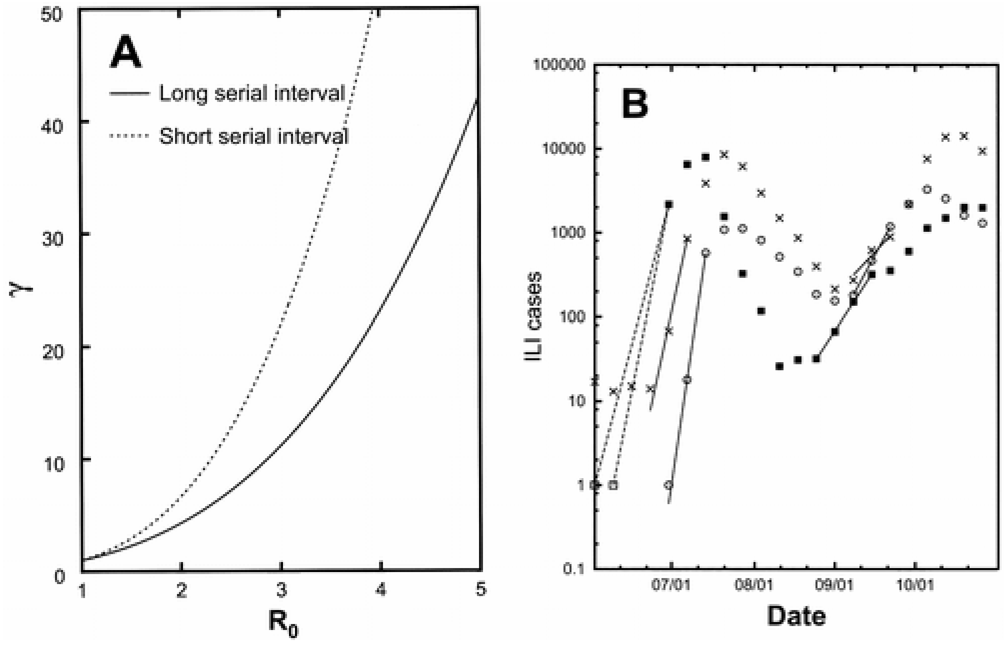

A
Long serial interval
Short serial interval
γ
R0
B
ILI cases
Date
07/01
08/01
09/01
10/01

Table 4. Estimates of reproduction number (R), by wave, in Copenhagen.

Data type	1918 summer wave R_{short} (2.6 days)	1918 summer wave R_{long} (4 days)	1918 fall wave R_{short} (2.6 days)	1918 fall wave R_{long} (4 days)
Cases of clinical influenza	2.2–2.4	2.8–3.0	1.22–1.24	1.29–1.33
Hospitalizations	2.8–4.0	3.6–5.4	1.2–1.3	1.3–1.4
Mortality due to respiratory disease[a]	. . .	. . .	1.4[b]	1.6[b]
Deaths attributable to all causes[a]	. . .	. . .	1.5[b]	1.8[b]

NOTE. R is estimated for the summer and fall waves in Copenhagen and is based on each data type (clinical influenza, hospitalizations, respiratory deaths, and deaths attributable to all causes) and 2 serial-interval parameter values—short duration (2.6 days) [4] and long duration (~4 days) [1]. Ranges represent 95% confidence intervals, on point estimates.

[a] The basic R for the summer wave could not be estimated with precision, when mortality data were used, because there were few deaths (see the Appendix, which is available in the online edition of the *Journal of Infectious Diseases*, for details).

[b] The method for R estimation based on excess mortality does not allow for computation of confidence intervals.

Estimation of R from mortality data

Based on C.E. Mills, J.M. Robins, M. Lipsitch (2004).
Transmissibility of 1918 pandemic influenza. *Nature* **432**, 904-906.

1. "max 1 week" based on the highest weekly growth factor observed during 2 consecutive weeks

2. "first 2 weeks" based on the growth factor of death counts during the first two weeks after the excess death rate had exceeded 1/100,000.

Finally $\gamma \to R$ as before.

Table A1. Number of deaths attributed to Spanish influenza during the 1918 fall waves and the corresponding estimates of the growth rate (γ) and the reproduction number (R).

	Copenhagen			Oslo	Stockholm	Gothenborg
	All causes of death [14]	Respiratory deaths [14]	Reported deaths from influenza or pneumonia [8]	Reported deaths from influenza or pneumonia [8]	Reported deaths from influenza or pneumonia [8]	Reported deaths from influenza or pneumonia [8]
Population, no.	543,000	534,000	534,000	260,000	413,000	197,000
Deaths/week, no.						
1 September	0	0	2	0	5	5
8 September	0	2	1	9[a]	7	2
15 September	0	4	5	10	16	8
22 September	0	8[a]	6[a]	23	41	30
29 September	10[a]	20	11	16	65	48
6 October	28	40	32	24	157	104
13 October	93	102	22	33	196	186
20 October	252	260	36	92	243	117
27 October	344	350	45	133	170	76
Estimated γ						
Max 1 week	3.3	2.6	2.9	2.8	2.6	3.8
First 2 weeks	9.3	5.0	5.3	2.6	NA	NA
Corresponding estimate of R (short-serial interval)						
Max 1 week	1.6	1.4	1.5	1.5	1.4	1.6
First 2 weeks	1.5	1.4	1.4	1.2	NA	NA
Corresponding estimate of R (long-serial interval)						
Max 1 week	1.8	1.6	1.7	1.7	1.6	1.9
First 2 weeks	1.7	1.5	1.5	1.3	NA	NA

NOTE. Low [8] did not include deaths attributed to bronchitis in Copenhagen. Also, the respiratory deaths and the reported deaths from influenza or pneumonia, in Copehagen, are determined by the use of a Serfling seasonal regression model, using weekly data. γ is determined in 2 ways, as proposed by [1]: the first row gives the maximal growth factor from 1 week to the next (max 1 week), and the last row gives the observed γ over the first 3 weeks after death counts exceeded the threshold level γ^2. NA, growth was not observed for 3 consecutive weeks or death counts never fell below threshold level between the summer and fall waves.

[a] This value indicates the first week in which deaths exceeded the threshold level of 1/100,000.

Some notable features from the analytic study

R_0 estimated from the summer wave was around 2.5 (bases on cases from general practitioners) or 4 (based on hospitalizations). This is higher than usually assumed.

R estimated from the fall wave as about 1.25 from both sources.

Why?

Conclusion for planning: In the summer the epidemic transmitted fast but would be hard to contain. Summer wave may have partially protected against fall wave.

Cause-deleted and cause-specific survival in infectious disease studies

Smallpox: Daniel Bernoulli 1760

Spanish flu: Canudas-Romo & Erlangsen 2008

Daniel Bernoulli 1760

Bernoulli, D. (1766) Essai d’une nouvelle analyse de la mortalité causée par la petite vérole. *Mém. Math. Phys. Acad. Roy. Sci., Paris, 1-45.*

Dietz, K. & Heesterbeek, J.A.P. (2002). David Bernoulli’s epidemiological model revisited. *Math. Biosc.* **180**, 1-21.

How much longer would we live if smallpox was eradicated?

Bernoulli assumed that smallpox acted like a censoring mechanism on deaths of other causes. He derived how Halley’s life table would be modified if smallpox was eradicated using a specific epidemic model.

$$\begin{tikzcd}
\text{Susceptible} \arrow[rr, "s(a)\lambda(a)"] \arrow[dr, "\mu(a)+\left\{1-s(a)\right\}\lambda(a)"'] & & \text{Immune} \arrow[dl, "\mu(a)"] \\
& \text{Dead} &
\end{tikzcd}$$

Change to Halley's lifetable

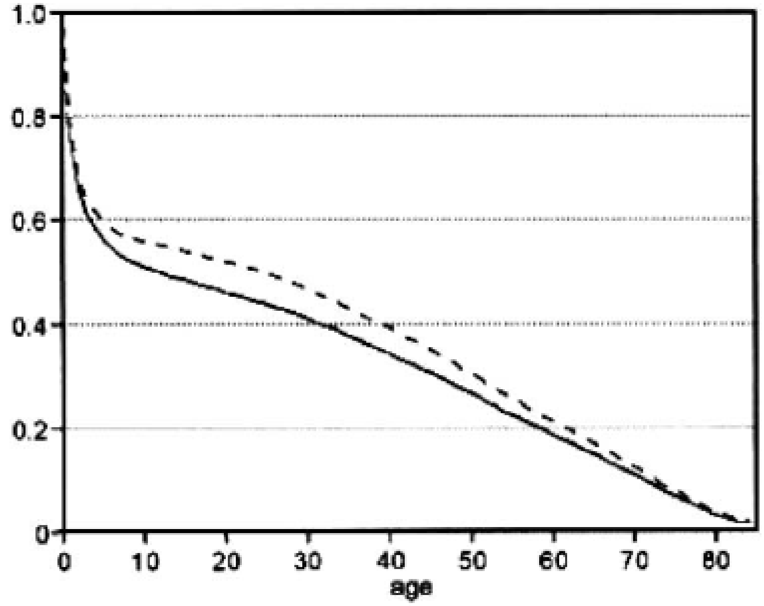


Fig. 4. The life table based on Halley in the state with smallpox (continuous line) and without smallpox (broken line). The median age would increase by 14 years from about 11.5 to 25.5 years!

Change in life expectancy if smallpox is eliminated

Bernoulli's results:

Life expectancy with smallpox = 26.58 years

Assuming case fatality = 0.125 and force of infection = 0.125/year, Bernoulli gets

Life expectancy without smallpox = 29.75 years.

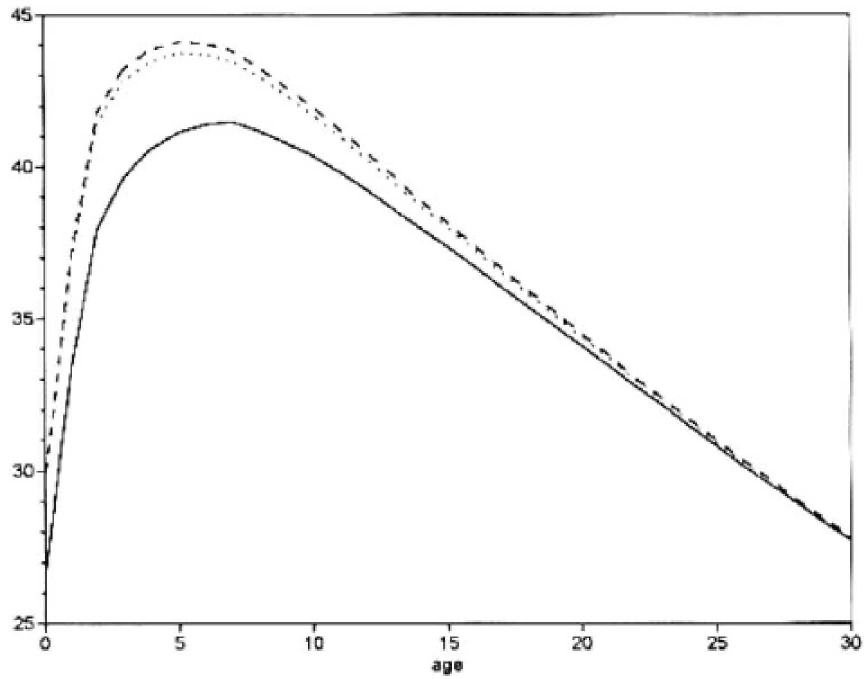


Fig. 6. The life expectancy of individuals who have survived a given age for Halley's table (with smallpox (continuous line) and without smallpox). The dotted line uses numerical integration (trapezoidal rule with yearly steps) and the broken line uses Eq. (32).

Cause-deleted survival: Recent demographic contributions

H. Beltrán-Sánchez, S. H. Preston, V. Canudas-Romo (2008). An integrated approach to cause-of-death analysis: cause-deleted life tables and decompositions of life expectancy. Presented at Population Association of America, New Orleans.

Mortality rates of cause *i* at time *t* and age *a*: $\mu_i\,(a,t),\ i = 1,\ldots k.$

Period survival functions $S_i(a,t) = \exp\left\{\int_0^a \mu_i(x,t)\,dx\right\}$

Suppress *t*

Total mortality rate $\mu(a) = \mu_1(a) + \ldots + \mu_k(a)$

Total survival function $S(a) = S_1(a)\ldots S_k(a)$

Define cause *i*-deleted survival function $S_{-i}(a) = S(a)/S_i(a)$

Life expectancy

Define life expectancy at age 0

$$e(0) = \int_0^\infty S(a)da$$

Life expectancy at birth if cause i is deleted.

$$e_{-i}(0) = \int_0^\infty S_{-i}(a)da$$

so years of life gained at birth if cause of death i were eliminated:

$$\begin{aligned} D_i(0) &= \int_0^\infty S_{-i}(a)da - \int_0^\infty S(a)da \\ &= \int_0^\infty S_{-i}(a)da - \int_0^\infty S_{-i}(a)S_i(a)da \end{aligned}$$

Denote differentiation wrt calendar time t by $\cdot$. Then

$$\dot{D}_i(0) = \int_0^\infty \dot{S}_{-i}(a)(1 - S_i(a))da - \int_0^\infty \dot{S}_i(a)S_{-i}(a)da.$$

Interpretation of calendar time change

$$\dot{D}_i(0) = \int_0^\infty \dot{S}_{-i}(a)(1 - S_i(a))da - \int_0^\infty \dot{S}_i(a)S_{-i}(a)da$$

Assume first (as Bernoulli) that survival from all other causes remains the same, i.e. $\dot{S}_{-i}(a) = 0$. Then the *change* in how much life expectancy is sacrificed to cause *i* is given by the *second term*.

Medical progress will make $\dot{S}_{-i}(a) > 0$ so $\dot{D}_i(0) < 0$ i.e. *less* life expectancy will be sacrificed to cause *i*.

However, in general $\dot{S}_{-i}(a) \neq 0$ and the *first term* may become important.

Illustration: cancer in the USA

	1970	2000	Difference	first term	second term
$e(0)$	70.70	76.96	6.26		

Gain $D_{-i}(0)$ eliminating cause *i*

i = cancer	2.54	3.27	0.73	1.00	-0.27
heart	6.20	3.93	-2.27	0.60	-2.87
all others	7.72	6.56	-1.14	1.98	-3.12

Cancer survival has *improved* from 1970 to 2000 but other causes have improved more. So years of life lost to cancer are *more* in 2000 than in 1970.

Spanish flu in Denmark in 1918

V. Canudas-Romo, A. Erlangsen (2008). Denmark: the lowest excess mortality during the influenza pandemic of 1918. Presented at Population Association of America meeting, New Orleans.

The ‘Spanish influenza’ hit world-wide in 1918.

Incidence W-age pattern.

Mortality primarily for 15-40 year old.

Cause of death ‘Tuberculosis and Influenza’.

		Observed	Influenza and tuberculosis eliminated	Difference
	Denmark	57.31	59.80	2.49
e_0 (1917)	Norway	57.75	61.91	4.16
	Sweden	58.90	62.40	3.50

		Observed	Influenza and tuberculosis eliminated	Difference
	Denmark	56.25	63.79	7.54
e_0 (1918)	Norway	50.30	59.55	9.25
	Sweden	49.81	61.98	12.17

			Due to Influenza and tuberculosis	Due to other causes
e_0 (1918)	Denmark	-1.06	-4.57	3.52
- e_0 (1917)	Norway	-7.45	-5.47	-1.98
	Sweden	-9.09	-8.75	-0.35

For Denmark: small decrease in life expectancy (1.06 years) from 1917 to 1918 despite 4.57 more years of life lost to influenza and tuberculosis. This is because there was *increase* in life expectancy due to deaths from other causes (3.52 years).
Perhaps the Spanish flu ‘killed’ weak Danes who would have died in 1918 from other causes (‘harvesting’).