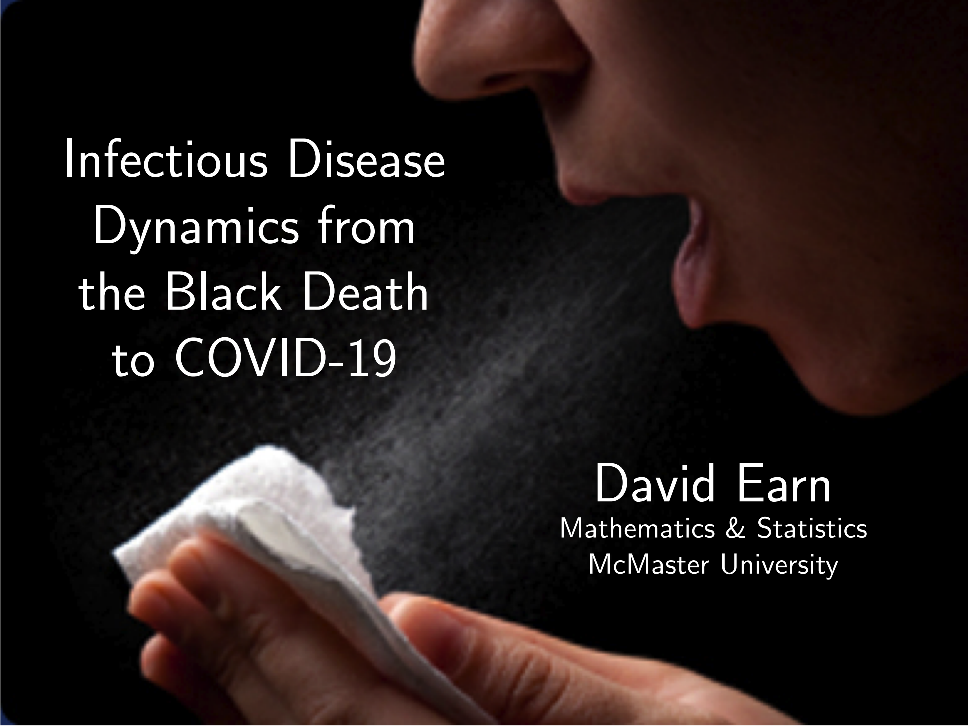


Infectious Disease Dynamics from the Black Death to COVID-19

David Earn
Mathematics & Statistics
McMaster University

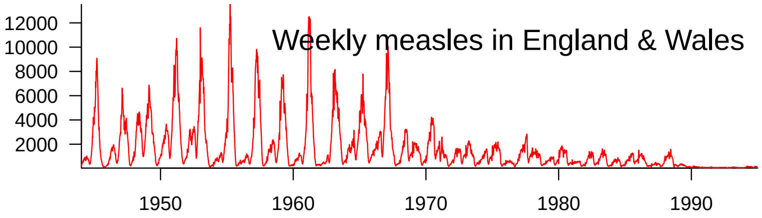
Outline

- Predicting patterns of epidemic recurrence
- Puzzles presented by plagues of the past
- Forecasting the future: modelling and policy

Outline

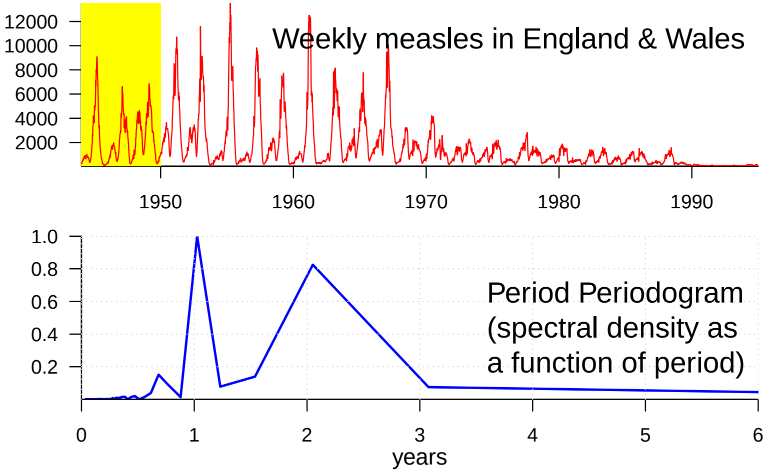
- **Predicting patterns of epidemic recurrence**
- Puzzles presented by plagues of the past
- Forecasting the future: modelling and policy

20th century measles dynamics in England and Wales

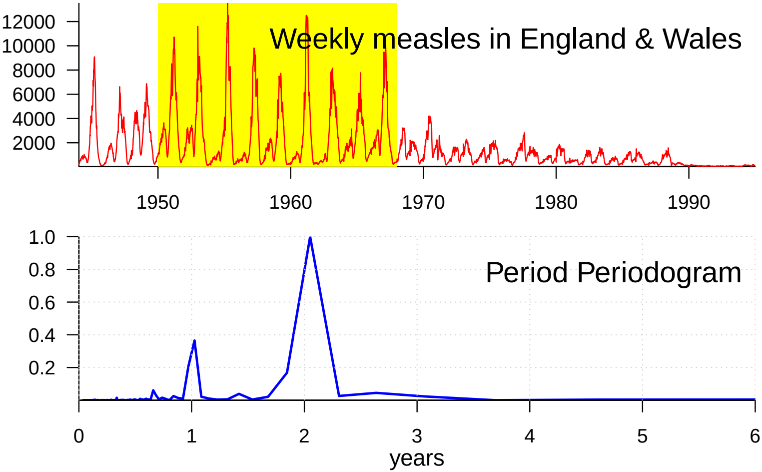


- Annual epidemics, then biennial, then irregular
- Why is the pattern of epidemic recurrence so complicated?
- What causes changes in frequency content over time?

What causes changes in frequency content over time?



What causes changes in frequency content over time?



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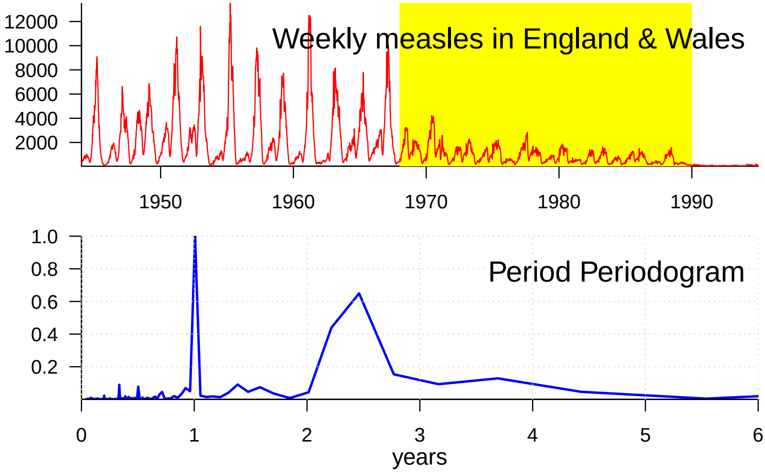
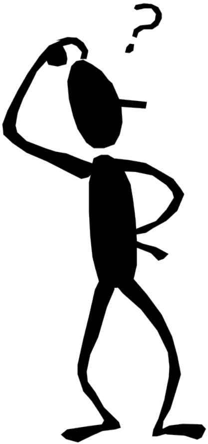
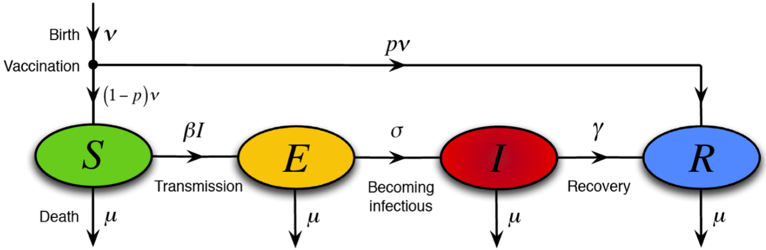


What causes changes in frequency content over time?



SEIR model



$$\frac{dS}{dt} = \nu(1-p) - \beta SI - \mu S$$

$$\frac{dE}{dt} = \beta SI - \sigma E - \mu E$$

$$\frac{dI}{dt} = \sigma E - \gamma I - \mu I$$

$$\frac{dR}{dt} = \nu p + \gamma I - \mu R$$

- Birth rate (ν for natality)
- Death rate (μ for mortality)
- Proportion vaccinated (p)

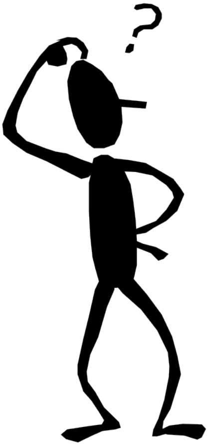
- Transmission rate (β)
- Mean latent period ($T_{\mathrm{lat}} = 1/\sigma$)
- Mean infectious period ($T_{\mathrm{inf}} = 1/\gamma$)

SEIR with vital dynamics and vaccination: Analysis

- Two Equilibria
  - Disease Free Equilibrium (DFE)
  - Endemic Equilibrium (EE)
- Periodic solutions ? Chaos? No.
- *Basic reproduction number $\mathcal{R}_0$*: expected infections from one infected entering a wholly susceptible population
  - Biological derivation: (assuming $\nu = \mu$ and $p = 0$)
    $\mathcal{R}_0 = \beta \times \frac{\sigma}{\sigma+\mu} \times \frac{1}{\gamma+\mu} \quad \simeq \beta\gamma^{-1} \quad \because \frac{1}{\mu} \gg \max\left(\frac{1}{\sigma}, \frac{1}{\gamma}\right)$
  - Mathematical derivation:
    $\mathcal{R}_0 = 1$ is stability boundary

    van den Driessche & Watmough 2002
    Mathematical Biosciences 180:29–48
- EE is globally asymptotically stable (GAS) if $\mathcal{R}_0 > 1$;
  DFE is GAS otherwise.
- Approach to EE is typically via *damped oscillations*.
- But observed recurrent epidemics are *undamped*.

What are we missing?



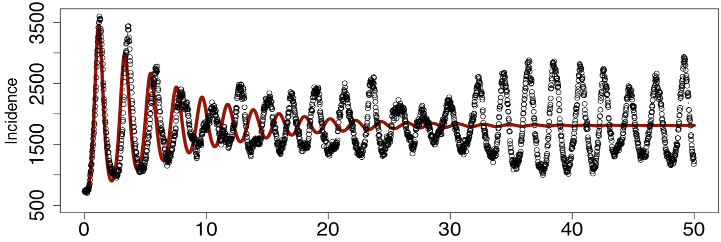
Populations are finite: demographic stochasticity

- Differential equations describe the expected behaviour in limit that population size $N \to \infty$
- Re-cast the SEIR model as a stochastic process (continuous time Markov jump process)
- Simulate with standard Gillespie algorithm

Gillespie 1976, *J. Comp. Phys.* **22**, 403–434

Gillespie Simulations: SEIR Results for Measles Parameters

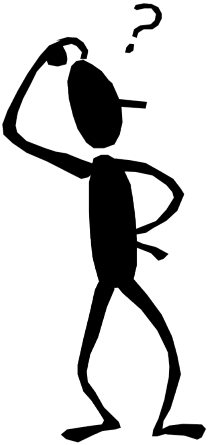
$\mathcal{R}_0 = 17$, $T_{\text{lat}} = 8$ days, $T_{\text{inf}} = 5$ days, $\nu = \mu = 0.02/\text{year}$, $N = 5,000,000$



Earn (2009) *IAS/Park City Mathematics Series* **14**:151–186

- Demographic Stochasticity sustains transient behaviour (oscillations do not damp out) (Bartlett 1950's)
- Explains undamped oscillations *at a single period*
- But, unable to explain changes in interepidemic period, or irregularity, as observed

What are we **STILL** missing?



Contact rates are higher during school terms!

Sinusoidal SEIR Model

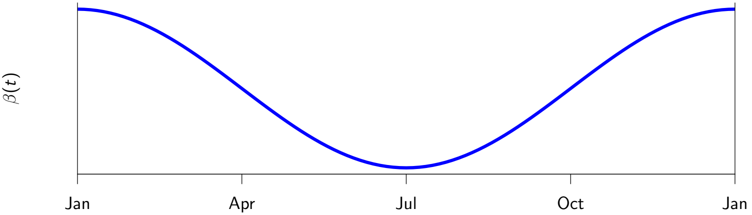
- Transmission rate β is not constant:
  high during school terms, low in summer

London WP, Yorke JA, 1973, *Am. J. Epidemiol.* **98**, 453–468

- For simplicity, model as a sine wave:

$$\beta(t) = \langle\beta\rangle \left(1 + \alpha \cos 2\pi t\right)$$

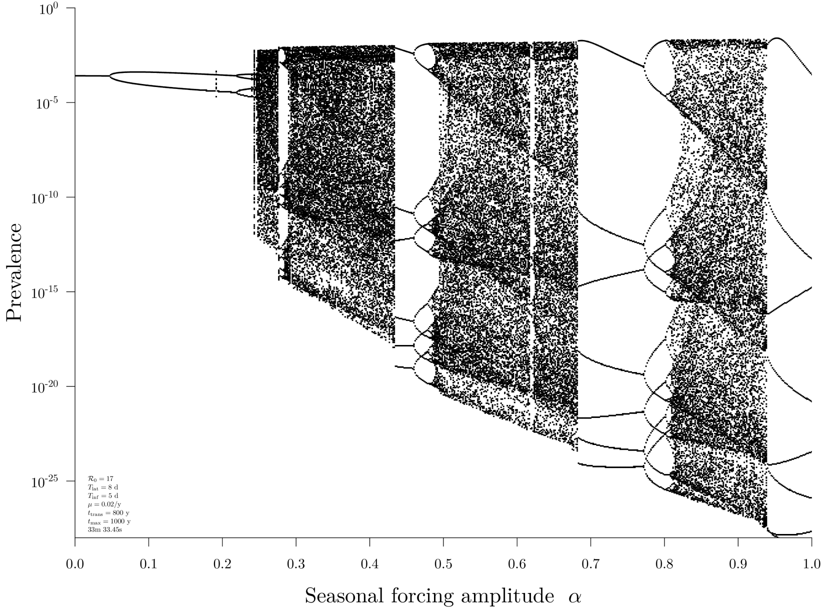
  - $\langle\beta\rangle =$ mean transmission rate
  - $\alpha =$ amplitude of seasonal variation in contact rate



Is this change significant?

- We now have a forced nonlinear system
- Forcing frequency can resonate with the natural timescales of the disease (*e.g.*, period of damped oscillations)
- Very rich dynamical system...
  (analogy: forced pendulum)

Measles Bifurcation Diagram (Sinusoidal SEIR model)



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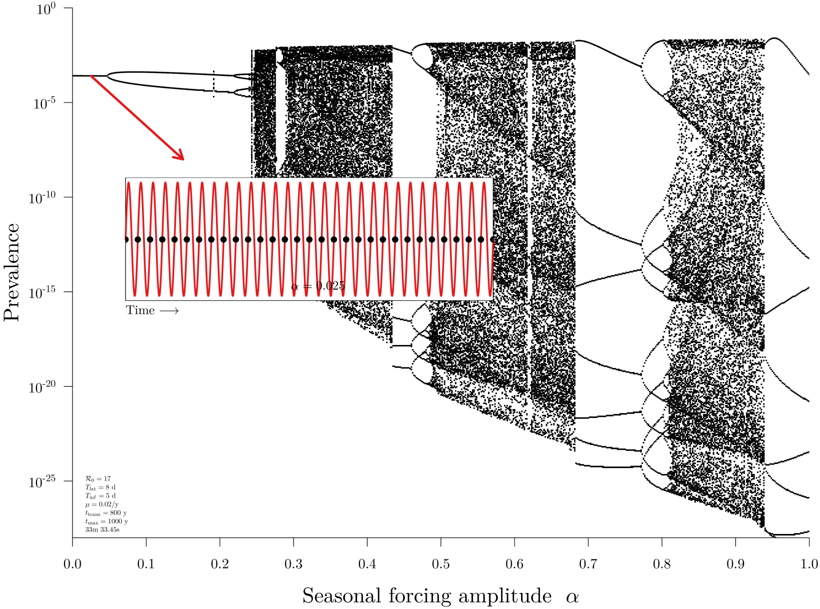

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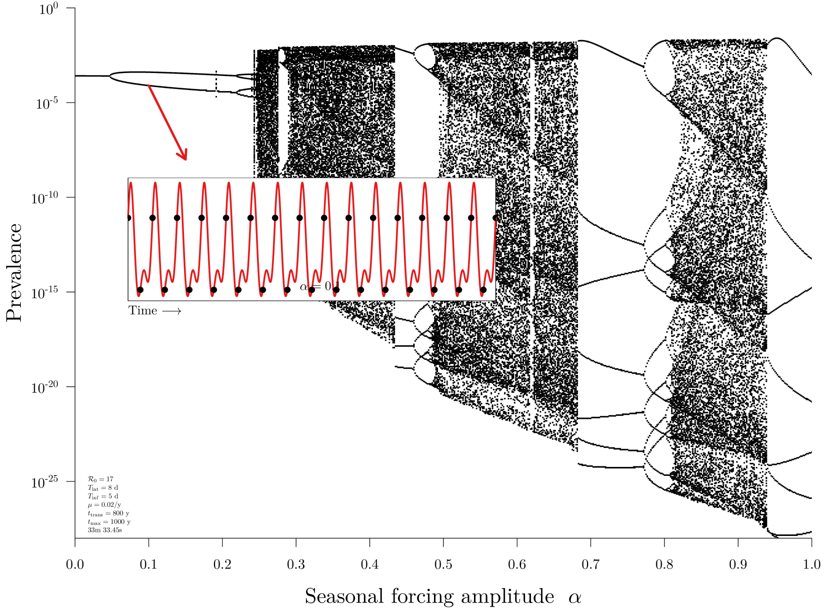

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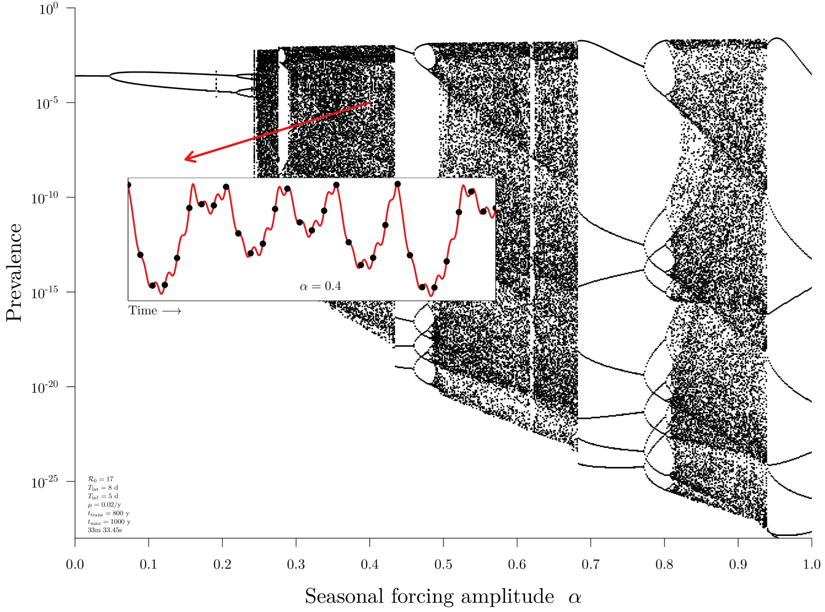


Sinusoidal SEIR Model: Does it explain measles dynamics?

SEIR model with sinusoidal forcing:

- Produces recurrent undamped epidemics of all frequencies observed in measles time series.

  Schwartz IB, Smith HL, 1983, *J. Math. Biol.* **18**, 233–253

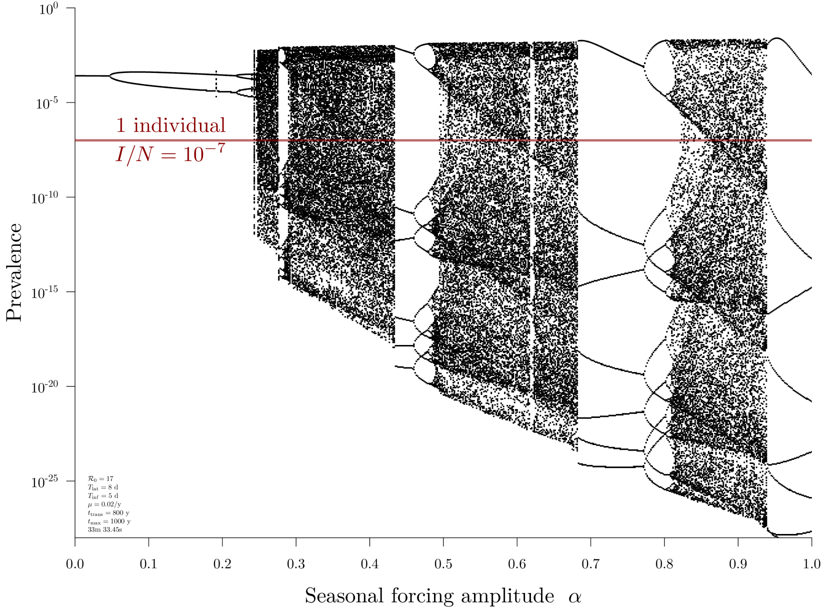
- Produces chaos, which can explain irregular behaviour and transitions from one type of cycle to another

  Olsen LF, Schaffer WM, 1990, *Science* **249**, 499–504

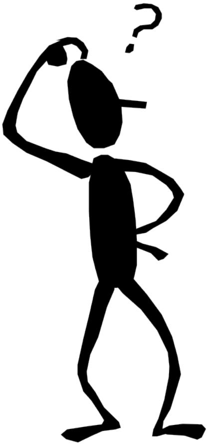
  - If correct, this implies these transitions are *unpredictable*.

- BUT... the model also predicts rapid extinction of the virus (not persistence).

Measles Bifurcation Diagram (Sinusoidal SEIR model)

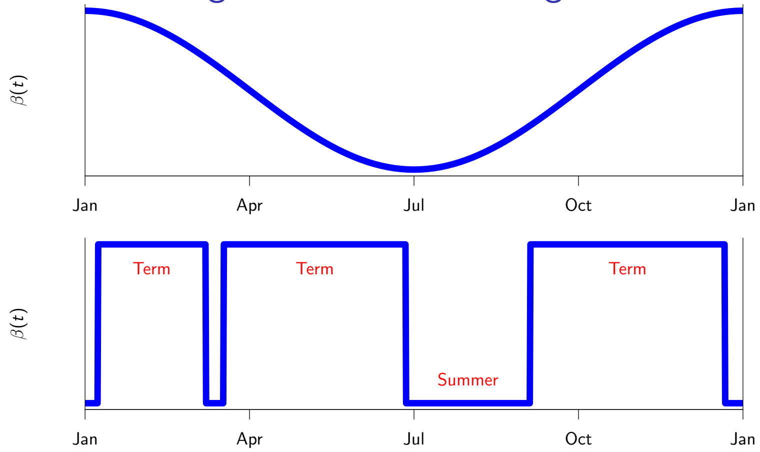


What are we **STILL** missing?



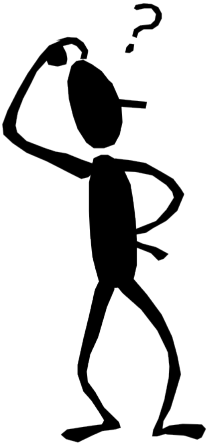
Contact rates are higher during **school terms!**

Sinusoidal forcing vs Term-time forcing



- <u>Term-time</u> SEIR model *predicts a strictly biennial cycle of measles epidemics, at all times and places*.
- Is superb agreement with post-war measles dynamics *coincidental???*

What **ELSE** might we be missing?



Key Insight

- Suppose $\mathcal{R}_0$ is estimated when the birth rate is ν.
- If the birth rate changes, $\nu \to \nu'$, then the dynamical effect is identical to changing $\mathcal{R}_0$ instead:

$$\mathcal{R}_0 \quad \longrightarrow \quad \mathcal{R}_0 \frac{\nu'}{\nu}$$

- More generally, any change in *susceptible recruitment rate* is equivalent dynamically to a change in $\mathcal{R}_0$.
- A change in birth rate $\nu \to \nu'$ together with a change in vaccine uptake $p \to p'$ is dynamically equivalent to

$$\mathcal{R}_0 \quad \longrightarrow \quad \mathcal{R}_0 \frac{\nu'(1-p')}{\nu(1-p)}$$

Earn *et al.* (2000) *Science* **287**:667–670
Earn (2009) *IAS/Park City Mathematics Series* **14**:151–186

Predicting Epidemic Transitions

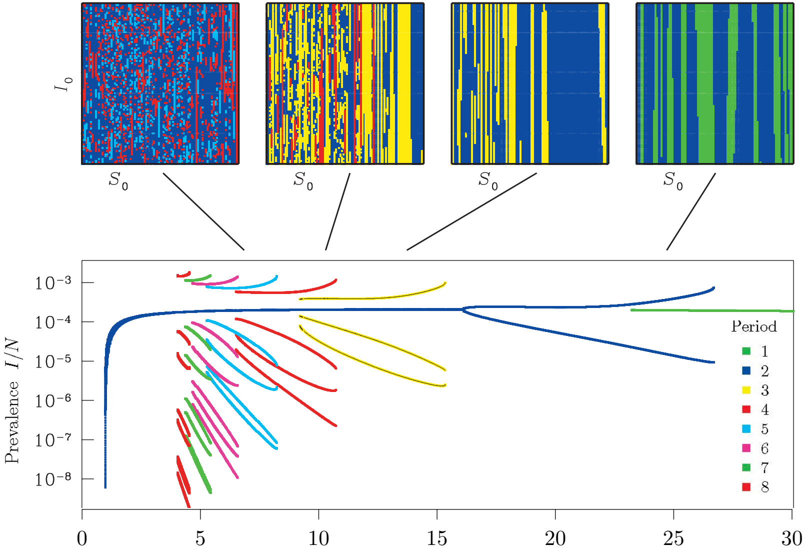
- Changes in
  - Birth rate (ν)
  - Vaccination proportion (p)
  - Transmission rate ($\langle\beta\rangle$ or $\mathcal{R}_0$)

  all map onto the same parameter axis.

- $\therefore$ Summarize possible dynamical changes induced by demographic/behavioural changes with a *one-parameter ($\mathcal{R}_0$) bifurcation diagram*.

- $\therefore$ Predict epidemic transitions by mapping observed changes in ν, p or $\mathcal{R}_0$ onto this diagram.

Measles Bifurcation Diagram (wrt $\mathcal{R}_0$)

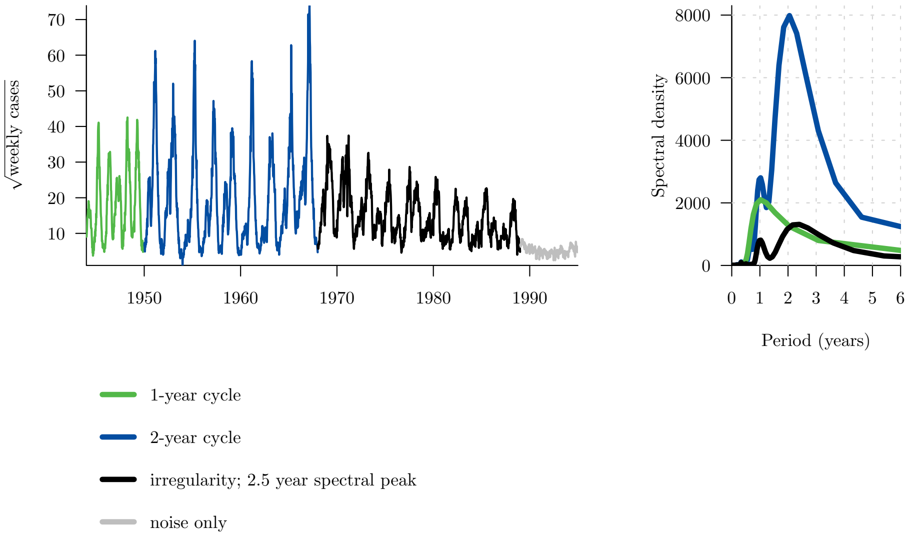


Low Birth Rate
High Vaccination

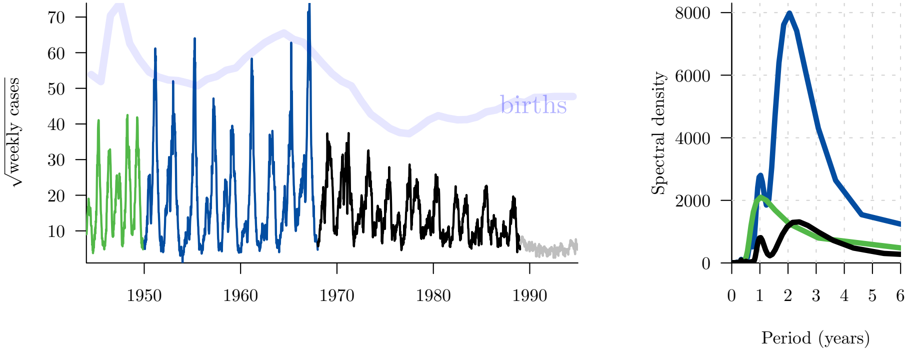
High Birth Rate
Low Vaccination

Earn *et al.* (2000) *Science* **287**:667–670

Measles in London, England



Measles in London, England



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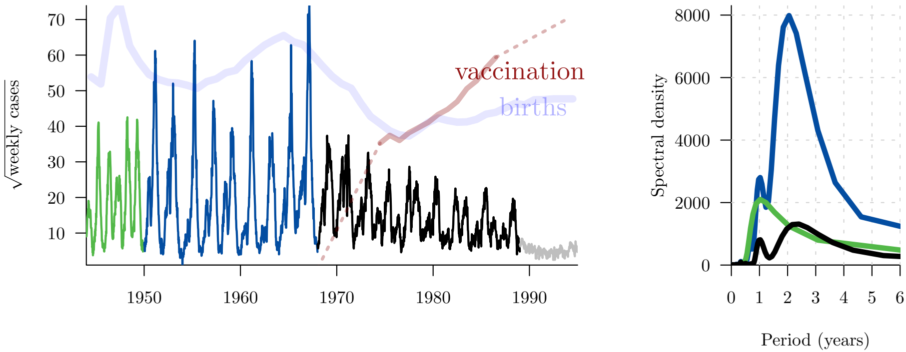

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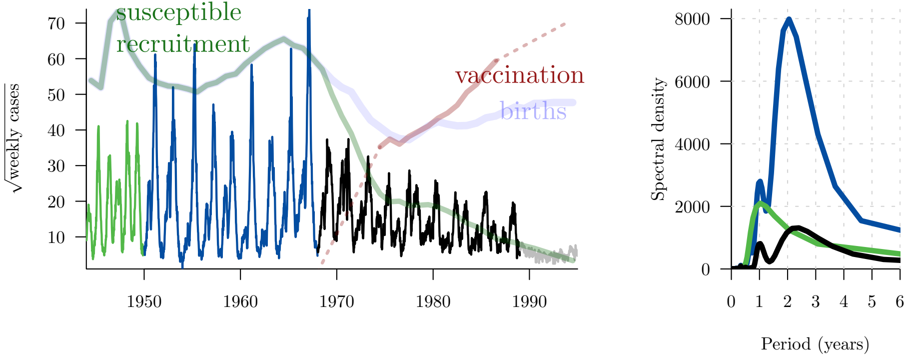

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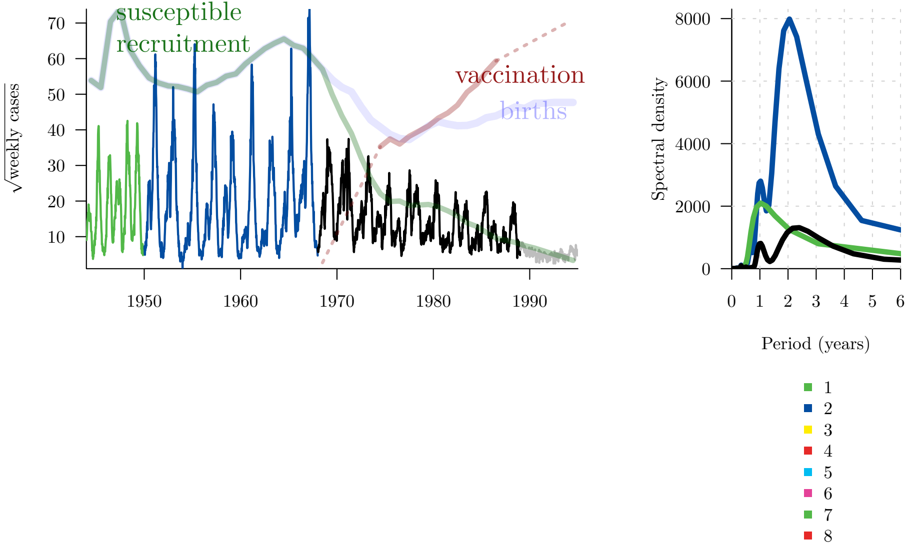

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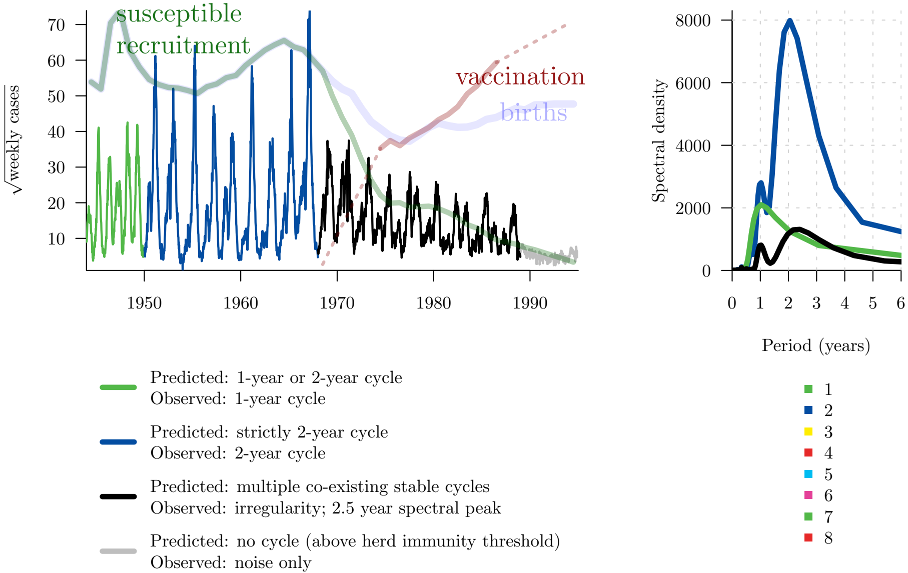
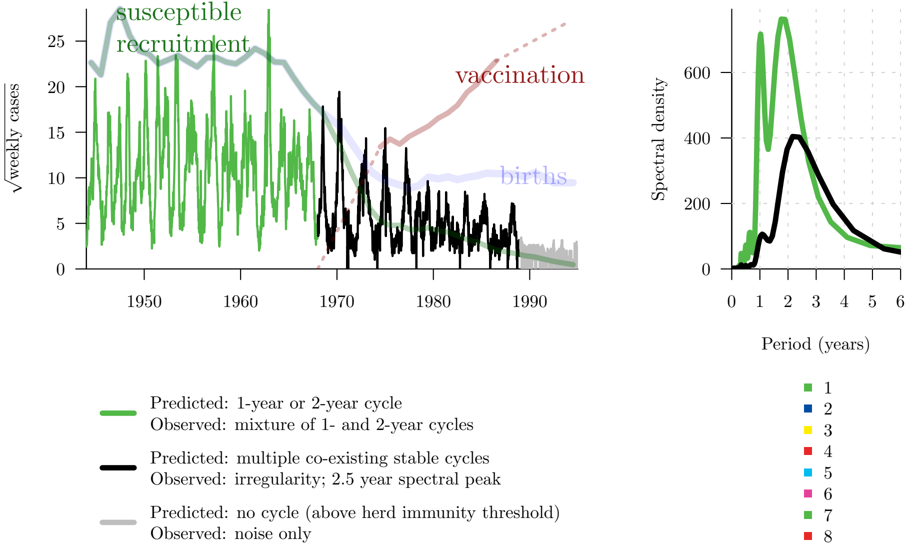
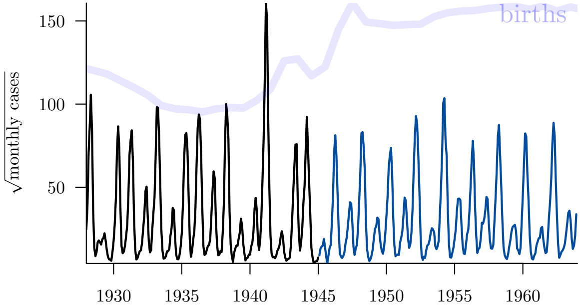
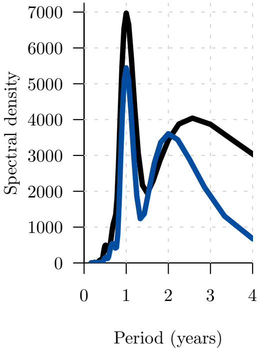


Measles in Liverpool, England



Measles in New York City

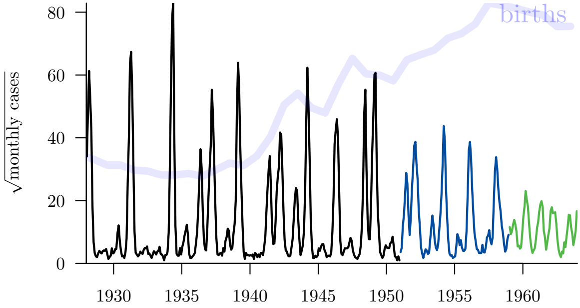


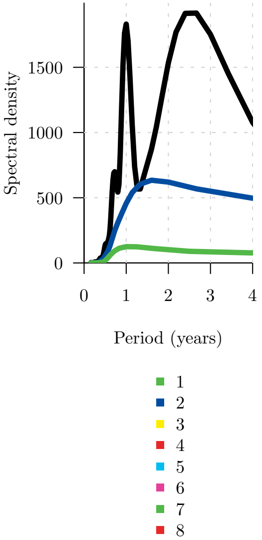


Predicted: multiple co-existing stable cycles
Observed: irregularity; 2.8 year spectral peak

Predicted: strictly 2-year cycle
Observed: 2-year cycle

Measles in Baltimore





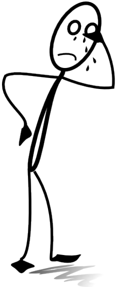
Predicted: multiple co-existing stable cycles
Observed: irregularity; 2.8 year spectral peak

Predicted: 1- or 2-year cycle
Observed: 2-year cycle

Predicted: 1- or 2-year cycle
Observed: 1-year cycle

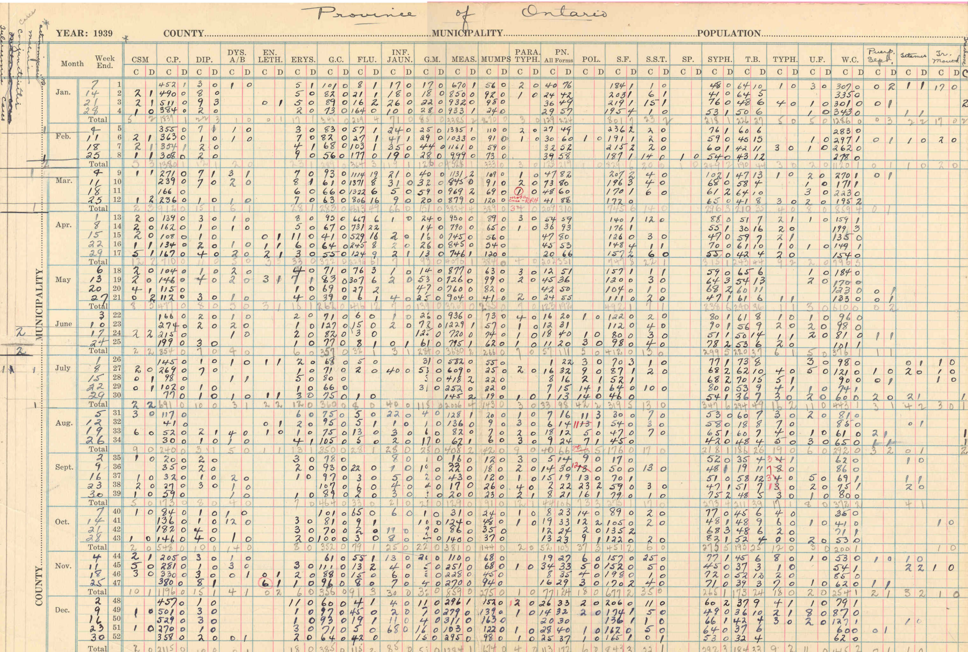
What about other notifiable childhood infectious diseases?

- Does same analysis explain patterns of recurrent epidemics for rubella? chicken pox? whooping cough?
- Alas! No!



- Only attractor of term-time SEIR model for rubella, chicken pox, or whooping cough is annual cycle.
- Yet these diseases show much more complex dynamics!

1939 weekly infectious disease notifications in Ontario



Province of Ontario

YEAR: 1939 COUNTY ... MUNICIPALITY ... POPULATION ...

Month	Week End.		CSM	C.P.	DIP.	DYS. A/B	EN. LETH.	ERYS.	G.C.	FLU.	INF. JAUN.	G.M.	MEAS.	MUMPS	PARA. TYPH.	PN. All Forms	POL.	S.F.	S.S.T.	SP.	SYPH.	T.B.	TYPH.	U.F.	W.C.	Puerp. Sept.	Tetanus	Tr. Mouth
			C D	C D	C D	C D	C D	C D	C D	C D	C D	C D	C D	C D	C D	C D	C D	C D	C D	C D	C D	C D	C D	C D	C D	C D	C D	C D
Jan.		1																										
		2																										
		3																										
		4																										
	Total																											
Feb.		5																										
		6																										
		7																										
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Mar.		9																										
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Apr.		13																										
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May		18																										
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June		22																										
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July		26																										
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Aug.		31																										
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Sept.		35																										
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Oct.		40																										
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Nov.		44																										
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	Total																											
Dec.		48																										
		49																										
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		51																										
		52																										
	Total																											

MUNICIPALITY

COUNTY

1939 weekly infectious disease notifications in Ontario

Province of Ontario

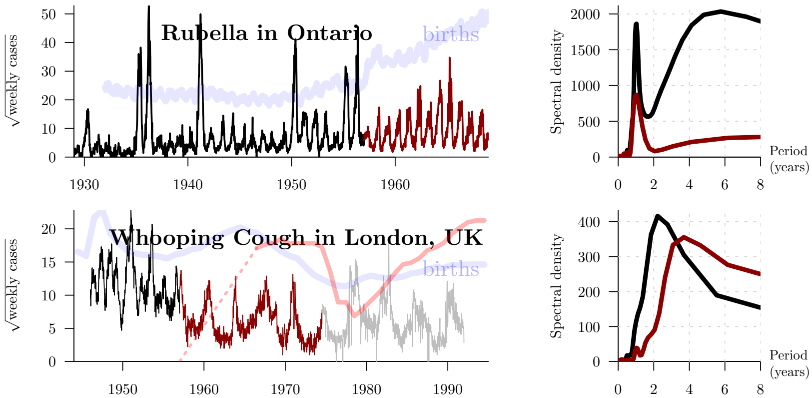
YEAR: 1939

Tularaemia cases	Conjunctivitis	Malaria	*Actinomycosis	Month	Day	Week	CSM C	CSM D	C.P C	C.P D	DIP. C	DIP. D	DYS. A/B C	DYS. A/B D	EN. LETH. C	EN. LETH. D	ERYS. C	ERYS. D	G.C. C	G.C. D	FLU. C	FLU. D	INF. JAUN. C	INF. JAUN. D	G.M. C	G.M. D	MEAS. C	MEAS. D
					7	1			452	1	3	0	1	0			5	1	101	0	8	1	17	0	17	0	670	1
				Jan.	14	2	2	1	490	0	8	0					5	0	82	0	21	1	18	0	18	0	850	0
					21	3	2	1	511	0	9	3			0	1	5	0	89	0	16	2	26	0	22	0	932	0
					28	4	1	0	384	0	2	0					2	0	73	0	164	0	10	0	28	0	933	1
					Total		5	2	1837	1	22	3	1	0	0	1	17	1	345	0	209	4	71	0	85	0	3385	2
			1		4	5			355	0	7	1	1	0			3	0	83	0	57	1	24	0	25	0	1335	1
				Feb.	11	6	2	1	363	0	1	0	1	0			7	0	82	0	27	1	41	1	29	0	1033	0
					18	7	2	1	354	1	2	0					4	1	68	0	103	1	35	0	44	0	1161	0
			1		25	8	1	1	308	0	2	0					9	0	56	0	177	0	19	0	28	0	999	0
			2		Total		5	3	1380	1	12	1	2	0			23	1	289	0	364	3	119	1	126	0	4528	1
		1			4	9	1	1	271	0	7	1	3	1			7	0	93	0	1114	19	21	0	40	0	1131	2
				Mar.	11	10			239	0	7	0	2	0			8	1	61	0	1371	8	31	0	32	0	845	0
					18	11			166	0							6	0	66	0	1322	6	5	0	59	0	969	2
					25	12	1	2	236	0	1	0	1	0			7	0	63	0	806	16	9	0	20	0	879	0
		1			Total		2	3	912	0	15	1	6	1			28	1	283	0	4613	49	66	0	151	0	3824	4
					1	13	2	0	139	0	3	0	1	0			8	0	95	0	667	6	1	0	24	0	950	0
				Apr.	8	14	2	0	162	0	1	0	1	0			5	0	67	0	731	22			14	0	790	0
					15	15	2	0	108	0	1	0			0	1	11	0	41	0	529	16	2	0	16	0	745	0
					22	16	1	1	134	0	2	0	1	0	1	1	6	0	64	0	245	8	2	0	26	0	845	0
					29	17	5	1	167	0	4	0	2	0	2	1	3	0	55	0	124	9	2	1	13	0	746	1
					Total		12	2	710	0	11	0	5	0	3	3	33	0	322	0	2296	61	7	1	93	0	4076	1
					6	18	2	0	104	0	1	0	2	0			4	0	71	0	76	3	1	0	14	0	877	0
				May	13	19	2	0	146	0	4	0	2	0	3	1	7	1	83	0	307	6	2	0	53	0	726	0
					20		4	1	115	0							1	0	69	0	27	2			47	0	760	0
					27	21	0	2	112	0	3	0	1	0			4	0	39	0	6	1	4	0	25	0	904	0
					Total		8	3	477	0	8	0	5	0	3	1	16	1	262	0	416	12	7	0	139	0	3267	0
					3	22			166	0	2	0	1	0			2	0	71	0	6	0	1	0	26	0	936	0
				June	10	23			274	0	2	0	2	0			1	0	127	0	15	0	2	0	72	0	1229	1
	2				17	24	2	2	215	0			1	0			2	0	82	0	3	0			125	0	720	0
					24	25			199	0	3	0					1	0	77	0	8	1	0	1	61	0	795	1

Month	Day	Week	MUMPS C	MUMPS D	PARA. TYPH. C	PARA. TYPH. D	PN. All Forms C	PN. All Forms D	POL. C	POL. D	S.F. C	S.F. D	S.S.T. C	S.S.T. D	SP. C	SP. D	SYPH. C	SYPH. D	T.B. C	T.B. D	TYPH. C	TYPH. D	U.F. C	U.F. D	W.C. C	W.C. D	Puerp. Sept. C	Puerp. Sept. D	Tetanus C	Tetanus D	M C
	7	1	56	0	2	0	40	76			184	1	1	0			48	0	64	10	1	0	3	0	307	0	0	2	1	1	1
Jan.	14	2	92	0	1	0	24	42			203	1	6	1			41	0	64	5					335	0					
	21	3	98	0			36	49			219	1	15	1			76	0	48	6	4	0	1	0	301	0	0	1			
	28	4	24	0			29	57			195	4	1	0			53	1	50	6			1	0	343	0			1	1	
	Total		270	0	3	0	129	224			801	7	23	2			218	1	226	27	5	0	5	0	1286	0	0	3	2	2	1
	4	5	110	0	2	0	27	49			236	2	2	0			76	1	60	6					283	0					
Feb.	11	6	91	0	1	0	30	60	1	0	191	1	2	0			59	0	45	15			1	0	297	1	0	1	1	0	
	18	7	59	0			32	52			215	2	2	0			60	1	42	11	3	0	1	0	262	0					
	25	8	73	0			39	58			187	1	14	0	1	0	54	0	43	12					278	0					
	Total		333	0	3	0	128	219	1	0	829	6	20	0	1	0	249	2	190	44	3	0	2	0	1120	1	0	1	1	0	
	4	9	109	0	1	0	47	82			207	2	4	0			102	1	47	13	1	0	2	0	270	1	0	1			
Mar.	11	10	91	0	2	0	73	80			196	3	4	0			68	0	58	4			1	0	171	1					
	18	11	69	0	0	0	48	60			170	1	6	0			61	2	64	10			3	0	223	0					
	25	12	120	0			41	88			172	0					65	0	41	8	3	0	2	0	195	2					
	Total		389	0	3	0	209	310			745	6	14	0			296	3	210	35	4	0	8	0	859	4	0	1			
	1	13	89	0	3	0	54	59			140	1	12	0			88	0	51	7	2	1	1	0	159	1					
Apr.	8	14	65	0	1	0	36	93			176	1					55	1	30	16	2	0			199	3					
	15	15	56	0			47	80			126	0	3	0			47	0	59	7	2	1			135	0					
	22	16	54	0			45	53			148	4	1	1			70	0	61	10	1	0	1	0	149	1					
	29	17	120	0			20	66			157	2	6	0			55	0	42	4	2	0			154	0					
	Total		384	0	4	0	202	351			747	8	22	1			315	1	243	44	9	2	2	0	796	5					
	6	18	63	0	3	0	12	51			157	1	1	1			59	0	65	6			1	0	184	0					
May	13	19	99	0	2	0	45	36			120	0	3	0			64	3	54	13			2	0	170	0					
	20		82	0			42	50			104	0	1	0			68	2	60	11					123	0	0	1			
	27	21	41	0	2	0	24	55			111	0	2	0			47	1	61	6	1	1			133	0	0	1			
	Total		285	0	7	0	123	192			492	1	7	1			238	6	240	36	1	1	3	0	610	0	0	2			
	3	22	73	0	4	0	16	20	1	0	122	0	2	0			80	1	61	8	1	0	1	0	96	0					
June	10	23	57	0	1	0	12	31			112	0	4	0			90	1	56	9	2	0	2	0	98	0					
	17	24	74	0	1	0	18	40	1	0	80	0	3	0			51	1	50	14	1	1	2	0	81	0	1	1			
	24	25	62	0	1	0	11	20	3	0	98	0	4	0			78	2	53	6	2	0			101	1					

Ontario 1939 | Template

Other Childhood Infections (not measles)

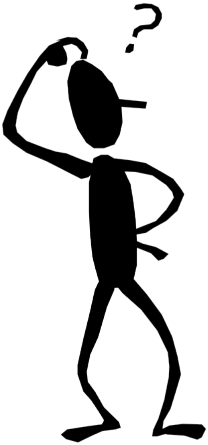


Incidence time series of these diseases show strong spectral peaks at periods not predicted by asymptotic analysis
(*i.e.*, **not** displayed by attractors of term-time SEIR model)

Bauch & Earn (2003) *Proc. R. Soc. Lond.* **270**:1573–1578

Argh!

What are we **STILL** missing?



Demographic Stochasticity Comes to the Rescue (Again!)

- Sustains transient behaviour
- *Linear perturbation theory* applied to the attractors of the model *explains other spectral peaks in data*
- *Whew!*

Get More Ambitious!

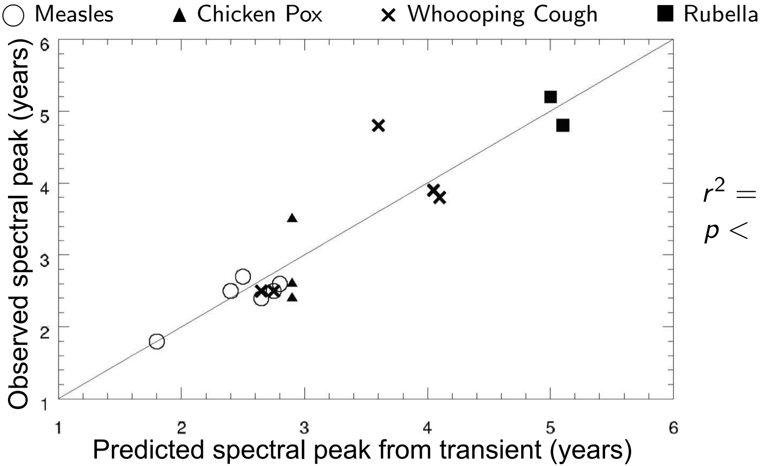
- Aim to predict all spectral peaks in the data
- Asymptotic analysis $\longrightarrow$ spectral peaks from attractors
- Perturbation analysis $\longrightarrow$ spectral peaks from transients

Bauch & Earn (2003) *Proc. R. Soc. Lond.* **270**:1573–1578

Krylova & Earn (2013) *J. R. Soc. Interface* **18**(10):20130098

Hempel & Earn (2015) *J. R. Soc. Interface* **12**(106):20150024

Predicted vs Observed Spectral Peaks from Transients



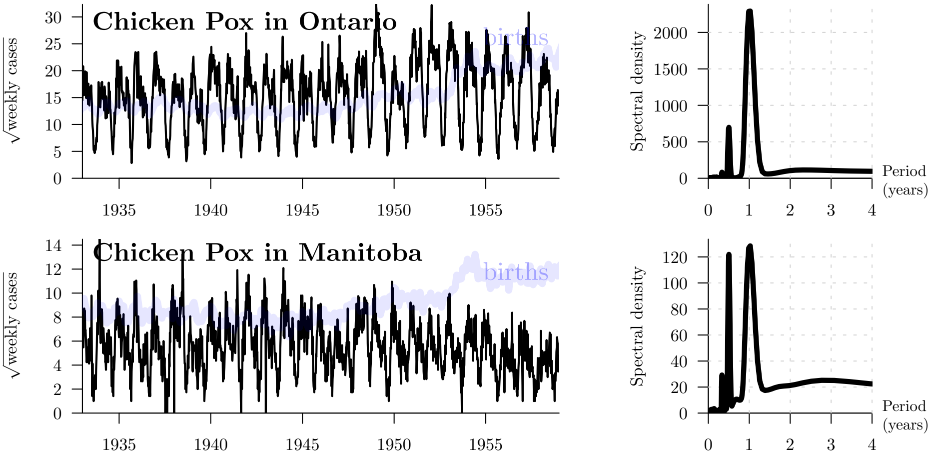
$r^2 = 0.83$
$p < 10^{-6}$

Bauch & Earn (2003) *Proc. R. Soc. Lond.* **270**:1573–1578

- Great! Can we successfully predict even more detail?

Can we predict magnitudes of spectral peaks?

Example:



- Population of MB $\ll$ ON

  $\Longrightarrow$ more demographic stochasticity

Modelling recurrent epidemics: Summary so far

- Good understanding of recurrent epidemic patterns of many infectious diseases in the 20th century
(*e.g.*, measles, chicken pox, whooping cough, rubella, . . .)
- *Perfect prediction* of spectral peaks *from attractors*
- *Excellent prediction* of spectral peaks *from transients*
- *Population size* is key determinant of *relative magnitude* of peaks from attractors vs. transients
(confirmed with stochastic simulations)

Modelling recurrent epidemics: Recent developments

- Extend time series further back in time
  - Does theory still allow us to predict epidemic transitions?
- Measles in New York City, 1891–1984
  - Success!

Hempel & Earn (2015) *J. R. Soc. Interface* **12**(106):20150024

- Key challenge that had to be overcome:
  changing patterns of seasonal variation in contact rates

Papst & Earn (2019) *J. R. Soc. Interface* **16**:20190202
Jagan *et al.* (2020) *PLoS Comp. Biol.* **16**(9):e1008124

- Smallpox in London, 1664–1930
  - Many observed epidemiological transitions, correlated with policy changes and historical events

Krylova & Earn (2020) *PLoS Biology* **18**(12):e3000506

  - Dynamical transition analysis in progress

Outline

- Predicting patterns of epidemic recurrence
- **Puzzles presented by plagues of the past**
- Forecasting the future: modelling and policy

The Diseases and Casualties this Week.

Abortive	6
Aged	50
Ague	1
Apoplexie	2
Childbed	42
Chrisomes	11
Cold	1
Consumption	99
Convulsion	63
Cough	1
Dropsie	22
Drownd at St. Martin in the Fields	1
Feaver	268
Fistula	2
Flox and Small-pox	4
Flux	1
Found dead in the Fields at St. Mary Islington	1
Frighted	1
Gowt	1
Grief	1
Griping in the Guts	35
Jaundies	2
Imposthume	8
Infants	9
Kingsevil	2
Meagrome	2
Plague	5533
Purples	2
Rickets	10
Rising of the Lights	13
Rupture	1
Scurvy	5
Spotted Feaver	65
Stilborn	10
Stone	3
Stopping of the stomach	6
Suddenly	1
Surfeit	36
Teeth	112
Thrush	3
Tissick	5
Vomiting	4
Winde	1
Wormes	12

Christned: Males 68, Females 78, In all 146.
Buried: Males 3212, Females 3248, In all 6460. Plague 5533

Decreased in the Burials this Week — 1837

Parishes clear of the Plague — 7 Parishes Infected — 123

The Assize of Bread set forth by Order of the Lord Maior and Court of Aldermen, A penny Wheaten Loaf to contain Nine Ounces and a half, and three half-penny White Loaves the like weight.

	Bur.	Plag.		Bur.	Plag.		Bur.	Plag.
St Alban Woodstreet	16	12	St George Botolphlane	1	1	St Martin Ludgate	12	10
Alhallows Barking	46	34	St Gregory by St Pauls	26	25	St Martin Orgars	8	5
Alhallows Breadstreet	1	1	St Hellen	6	5	St Martin Outwitch	6	5
Alhallows Great	42	41	St James Dukes place	27	23	St Martin Vintrey	44	44
Alhallows Honylane			St James Garlickhithe	16	12	St Matthew Fridaystreet		
Alhallows Lesse	17	17	St John Baptist	11	10	St Maudlin Milkstreet	4	4
Alhallows Lumbardstreet	5	5	St John Evangelist			St Maudlin Oldfishstreet	8	6
Alhallows Staining	21	18	St John Zachary	12	9	St Michael Bassishaw	10	7
Alhallows the Wall	33	28	St Katharine Coleman	20	16	St Michael Cornhil	4	3
St Alphage	13	5	St Katharine Crechurch	34	29	St Michael Crookedlane	15	1[illegible]
St Andrew Hubbard	4		St Lawrence Jewry	6	5	St Michael Queenhithe	25	2[illegible]
St Andrew Undershaft	16	14	St Lawrence Pountney	14	10	St Michael Quern	4	3
St Andrew Wardrobe	30	24	St Leonard Eastcheap	3	3	St Michael Royal	20	1[illegible]
St Ann Aldersgate	28	27	St Leonard Fosterlane	16	13	St Michael Woodstreet	6	3
St Ann Blackfryers	57	50	St Magnus Parish	5	4	St Mildred Breadstreet	4	4
St Antholins Parish	7	4	St Margaret Lothbury	7	6	St Mildred Poultrey	4	2
St Austins Parish	4	3	St Margaret Moses			St Nicholas Acons	4	[illegible]
St Bartholomew Exchange	7	7	St Margaret Newfishstreet	18	13	St Nicholas Coleabby	8	[illegible]
St Bennet Fynck	4	2	St Margaret Pattons	4	3	St Nicholas Olaves	8	[illegible]
St Bennet Gracechurch	4	2	St Mary Abchurch	7	5	St Olave Hartstreet	13	[illegible]
St Bennet Paulswharf	15	7	St Mary Aldermanbury	14	14	St Olave Jewry	5	[illegible]
St Bennet Sherehog	2		St Mary Aldermary	4	4	St Olave Silverstreet	4	[illegible]
St Botolph Billingsgate	8	8	St Mary le Bow	1	1	St Pancras Soperlane	1	
Christs Church	44	39	St Mary Bothaw	6	4	St Peter Cheap	3	
St Christophers	4	4	St Mary Colechurch	3	1	St Peter Cornhil	8	
St Clement Eastcheap	1	1	St Mary Hill	11	8	St Peter Paulswharf	10	
St Dionis Backchurch	9	2	St Mary Mounthaw	4	3	St Peter Poor	8	
St Dunstan East	28	24	St Mary Sommerset	44	38	St Steven Colemanstreet	43	
St Edmund Lumbardstr.	3	1	St Mary Stayning	3	2	St Steven Walbrook	2	
St Ethelborough	7	4	St Mary Woolchurch	7	4	St Swithin	6	
St Faith	8	6	St Mary Woolnoth	7	5	St Thomas Apostle	8	
St Foster	8	6	St Martin Iremongerlane	2	2	Trinity Parish	10	
St Gabriel Fenchurch	3	3						

Christned in the 97 Parishes within the Walls — 39 *Buried* — 1149 *Plague* — 94[illegible]

	Bur.	Plag.		Bur.	Plag.		Bur.	Plag.
St Andrew Holborn	173	151	St Botolph Aldgate	372	338	Saviours Southwark	364	[illegible]
St Bartholomew Great	17	15	St Botolph Bishopsgate	153	121	S. Sepulchres Parish	137	[illegible]
St Bartholomew Lesse	7	7	St Dunstan West	63	59	St Thomas Southwark	40	[illegible]
St Bridget	92	67	St George Southwark	140	133	Trinity Minories	24	[illegible]
Bridewel Precinct	23	23	St Giles Cripplegate	196	151	At the Pesthouse	8	[illegible]
St Botolph Aldersgate	71	64	St Olave Southwark	378	281			

Christned in the 16 Parishes without the Walls — 45 *Buried, and at the Pesthouse* — 2258 *Plague* — 1[illegible]

	Bur.	Plag.		Bur.	Plag.		Bur.	Plag.
St Giles in the fields	95	78	Lambeth Parish	49	39	St Mary Islington	35	[illegible]
Hackney Parish	14	12	St Leonard Shoreditch	95	91	St Mary Whitechappel	32[illegible]	[illegible]
St James Clerkenwel	48	42	St Magdalen Bermondsey	128	106	Rotherith Parish	21	[illegible]
St Kath. near the Tower	55	39	St Mary Newington	81	81	Stepney Parish	67[illegible]	[illegible]

Christned in the 12 out Parishes in Middlesex and Surry — 40 *Buried* — 1623 *Plague* — 1[illegible]

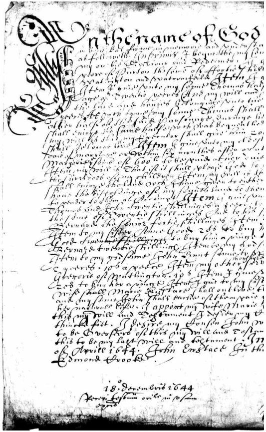
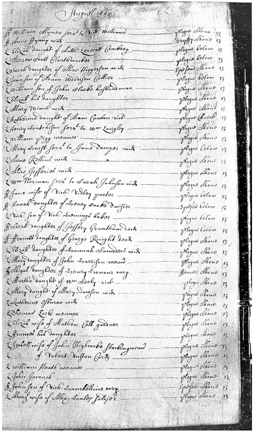
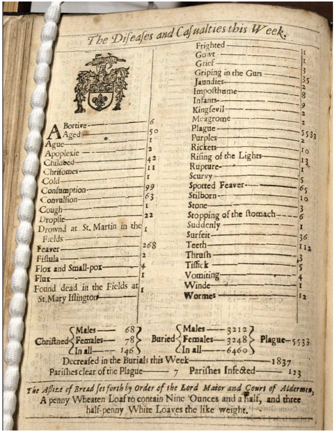
	Bur.	Plag.		Bur.	Plag.		Bur.	Plag.
St Clement Danes	128	110	St Martin in the fields	209	143	St Margaret Westminster	30[illegible]	[illegible]
St Paul Covent Garden	25	24	St Mary Savoy	19	16	Whereof at the Pesthouse	[illegible]	

Christned in the 5 Parishes in the City and Liberties of Westminster — 18 *Buried* — 690 *Plague* — [illegible]

M

Frighted	1
Gowt	1
Grief	3
Griping in the Guts	35
Jaundies	2
Impoſthume	8
Infants	9
Kingſevil	2
Meagrome	2
Plague	5533
Purples	2
Rickets	10

Sources of mortality data for London, England

Wills	Parish Registers	Bills of Mortality
		
since 1258	since 1538	since 1563 (continuous since 1661)

Will image:

Parish register image:

Bill of Mortality image:

The Diseases and Casualties this Week.

Abortive	6	Frighted	1
Aged	50	Gowt	1
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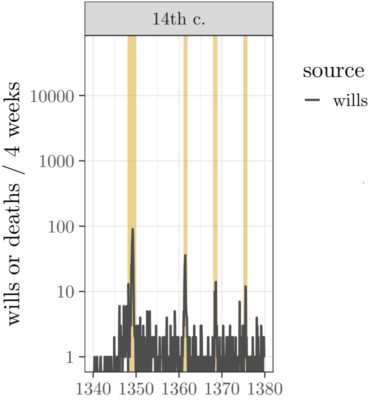
Earn, Ma, Poinar, Dushoff, Bolker (2020) *PNAS* **117**:27703–27711

Mortality in London, England, 1348–1680



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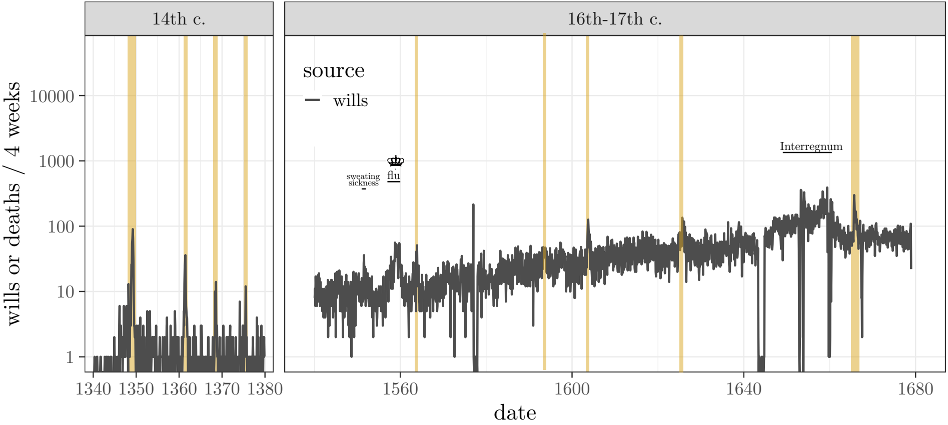

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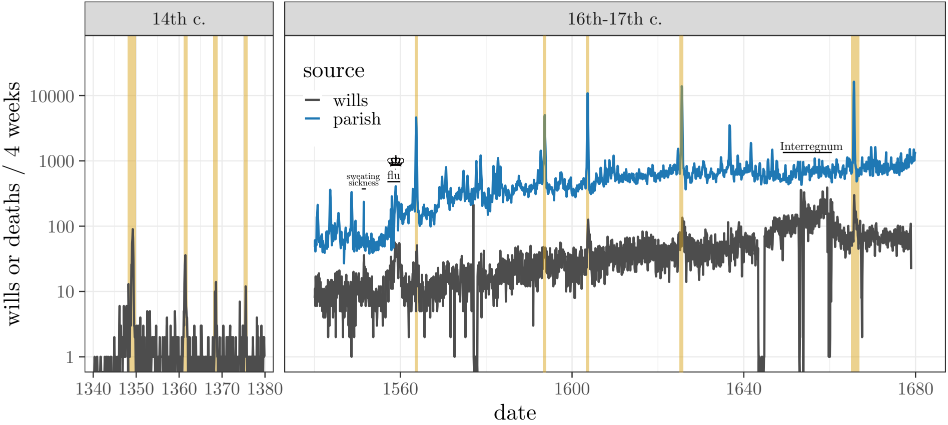

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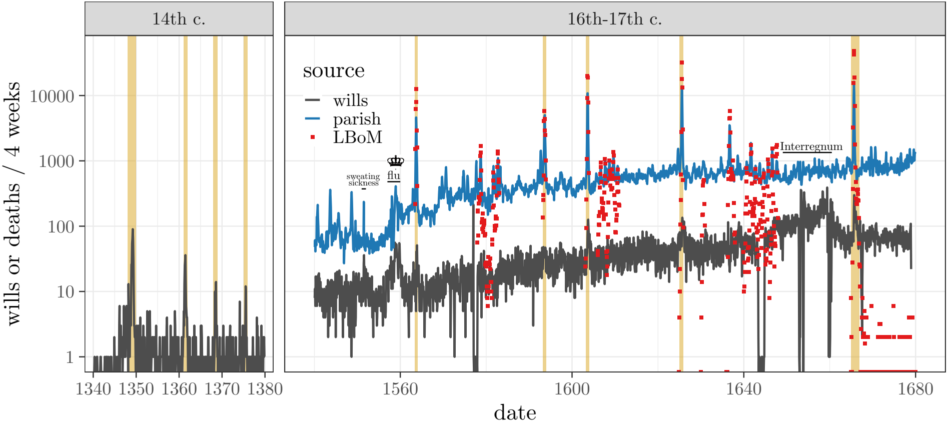
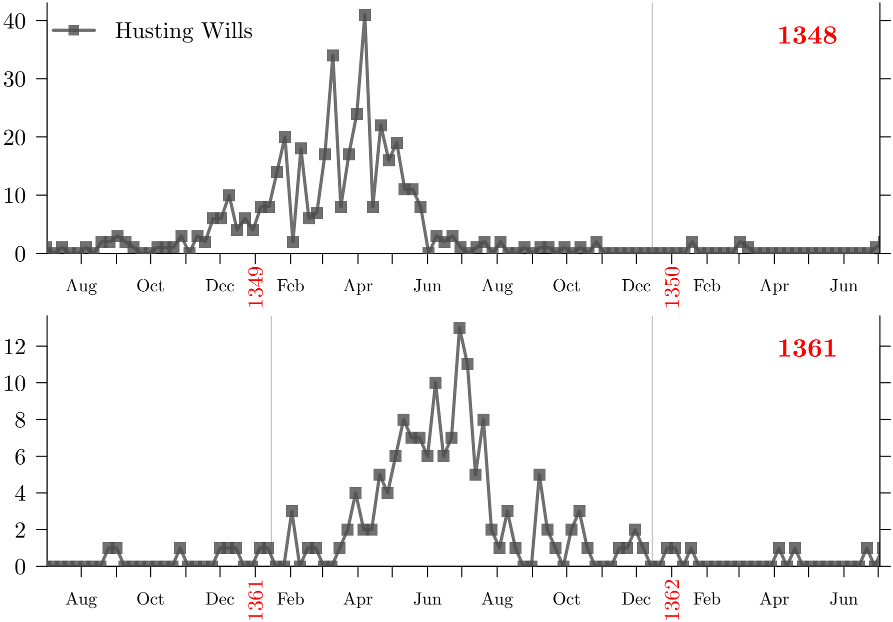


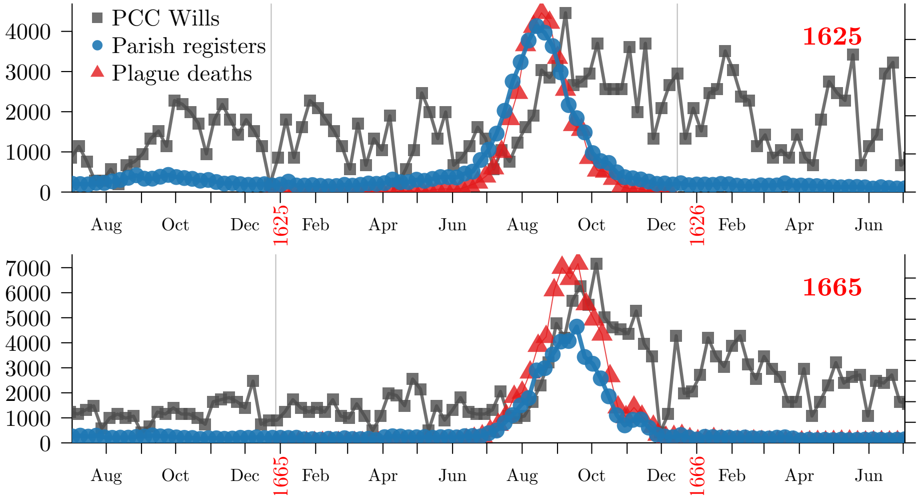
Earn, Ma, Poinar, Dushoff, Bolker (2020) *PNAS* **117**:27703–27711

14th c. plague epidemics in London



Earn, Ma, Poinar, Dushoff, Bolker (2020) *PNAS* **117**:27703–27711

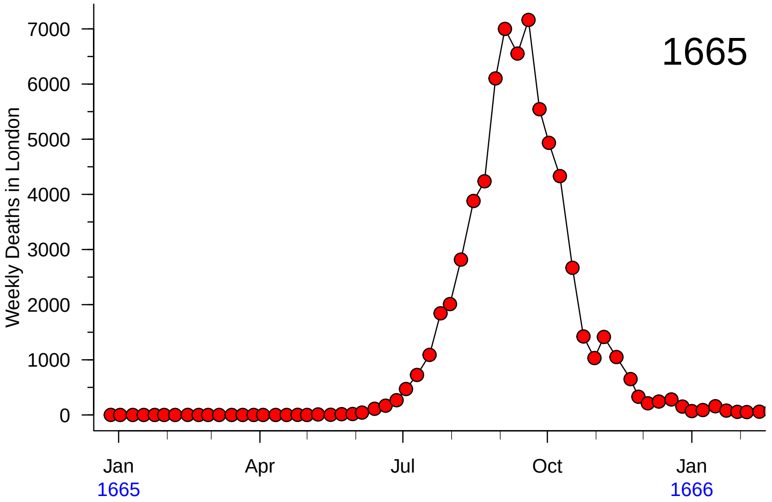
17th c. plague epidemics in London



Earn, Ma, Poinar, Dushoff, Bolker (2020) *PNAS* **117**:27703–27711

Is it OK to compare results based on wills with results from mortality data?

Plague in London



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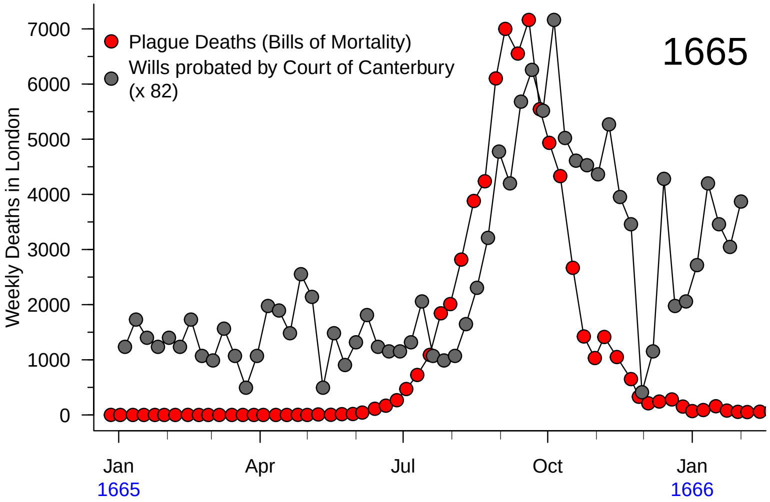
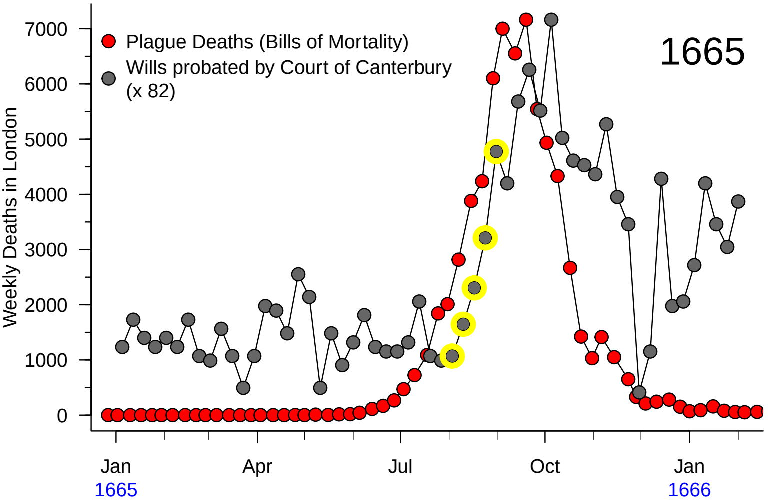


Plague in London

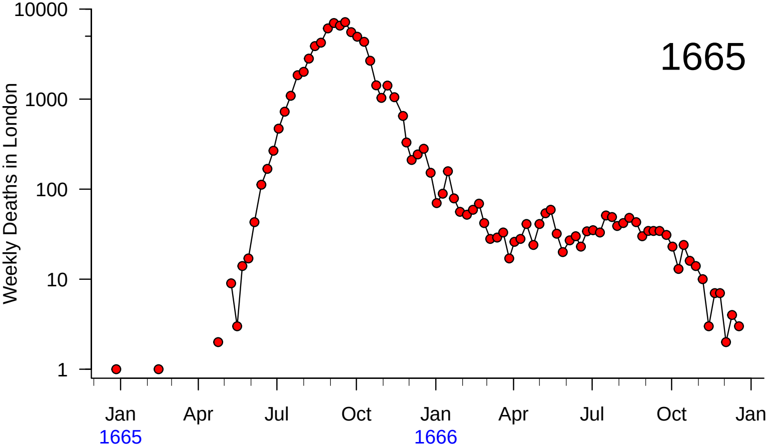


Compare growth rates of plague epidemics in London

- Property of the epidemic curve (*the data alone*)
- Estimate without assumptions about processes that generated the data (since we don't know the mode of transmission)
  - *human-to-human* (pneumonic plague)
  - *rat-to-flea-to-human* (bubonic plague)

Estimating the initial growth rate of an epidemic

- Naïvely, we just fit a straight line to the log of the mortality time series.



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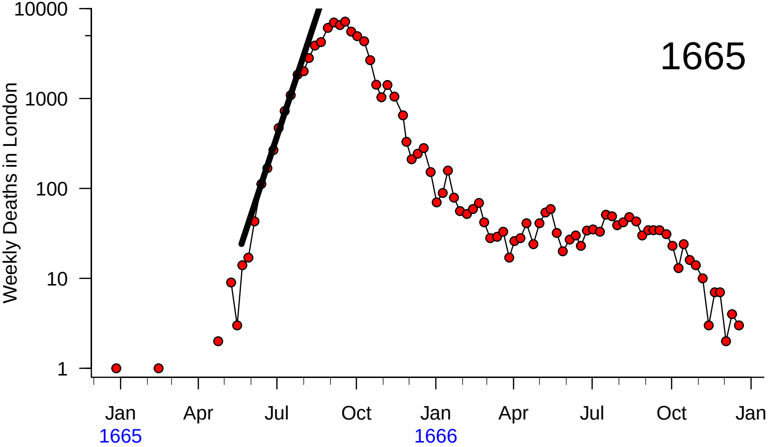

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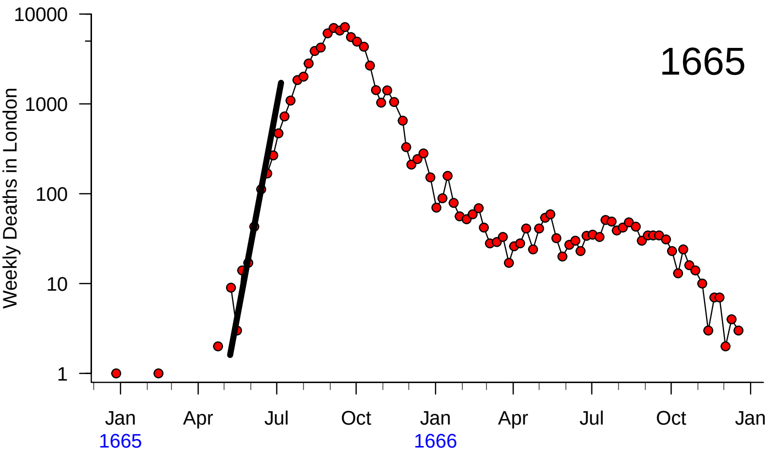
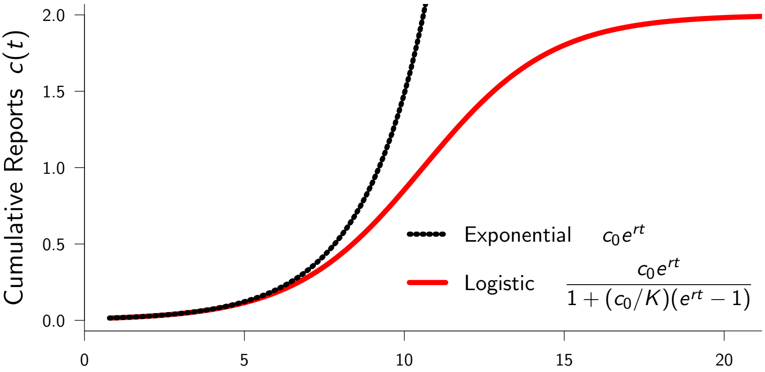


Estimating the initial growth rate of an epidemic

Instead fit a **saturating** rather than a **purely exponential** curve.



- Both curves have same initial exponential growth rate r.
- Test extensively using simulated epidemics for which we know the correct answer.

Ma, Dushoff, Bolker, Earn (2014) *Bull. Math. Biol.* **76**:245–260

Initial growth rates for plague in London, 1348–1665

- Later plagues grew 4$\times$ faster than early plagues!

  Doubling time:
  - In 1348: $\sim$ 45 days
  - In 1665: $\sim$ 11 days

- **Why** did plague epidemics "accelerate"?
  - Evolution of increased infectiousness? longer infectious period?
  - Changes in population density? social structure? contact patterns?
  - Changes in weather?
  - Bubonic *vs.* pneumonic plague?

Earn, Ma, Poinar, Dushoff, Bolker (2020) *PNAS* **117**:27703–27711

Bubonic or pneumonic plague?

Suppose pneumonic plague during second pandemic was exactly like modern pneumonic plague.

- Pneumonic in 14th century London?
  $\Longrightarrow$ $\sim$ 20% of population infected

  BUT $\sim$ 30–50% *of total population died in 1348*

  $\Longrightarrow$ early plagues probably not (primarily) pneumonic

- A remarkable inference to be able to make based on counting wills! (and a little mathematical modelling)

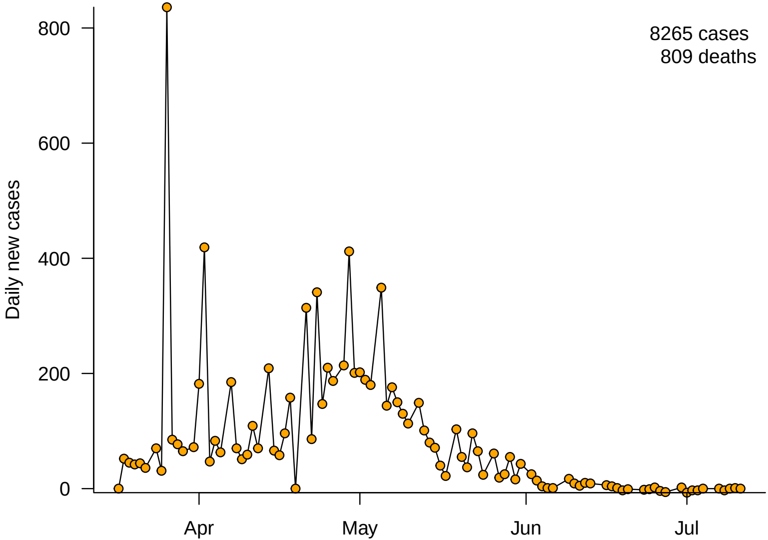
Earn, Ma, Poinar, Dushoff, Bolker (2020) *PNAS* **117**:27703–27711

Outline

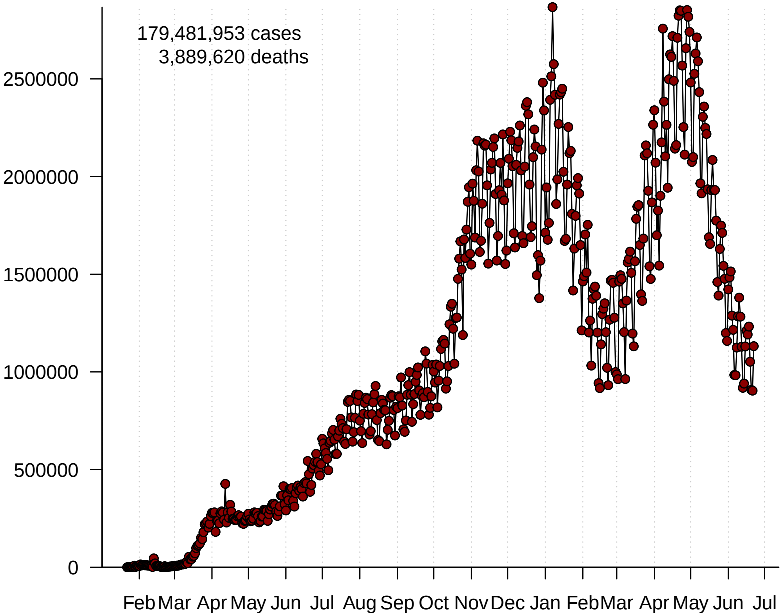
- Predicting patterns
  of epidemic recurrence
- Puzzles presented by
  plagues of the past
- **Forecasting the future:
  modelling and policy**

SARS

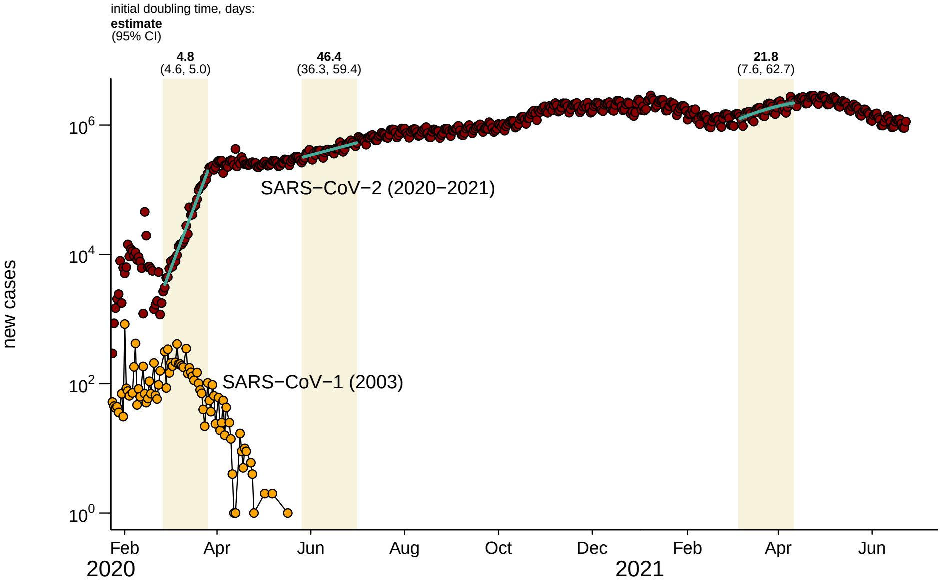
Daily SARS-CoV-1 in 2003 (Worldwide)



Daily SARS-CoV-2 in 2020–2021 (Worldwide)

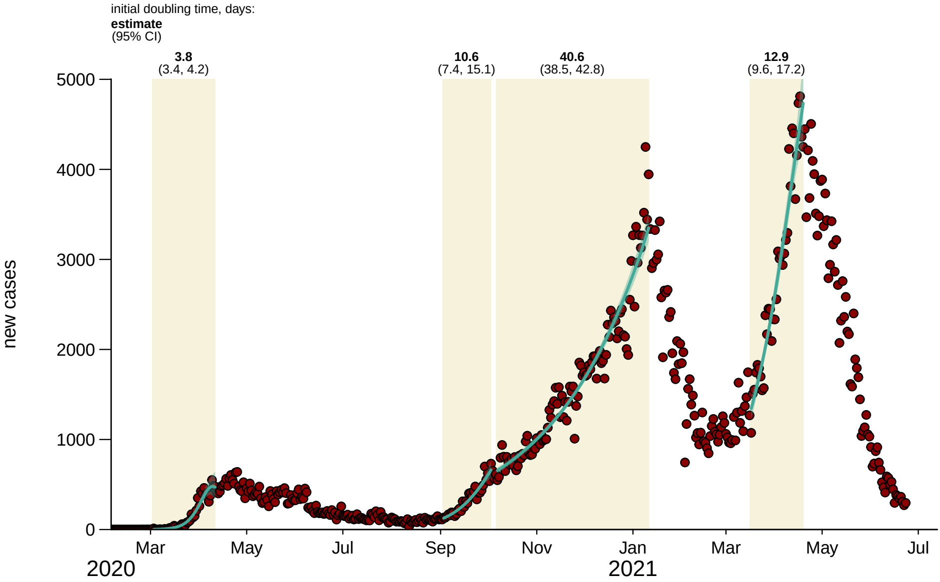


Daily SARS-CoV-2 vs SARS-CoV-1 (Worldwide)



SARS-CoV-2
in Ontario

COVID-19 cases in Ontario



Modelling SARS-CoV-2 / COVID-19

Much richer data (compared with historical epidemics):

- Daily counts of positive tests, hospital occupancy, ICU occupancy, deaths, ...
- Daily vaccine doses administered
- Daily measures of weather, mobility
- Info on policy changes, travel restrictions, new virus variants, ...

Harder problem:

- Forecast the future!

Modelling SARS-CoV-2 / COVID-19

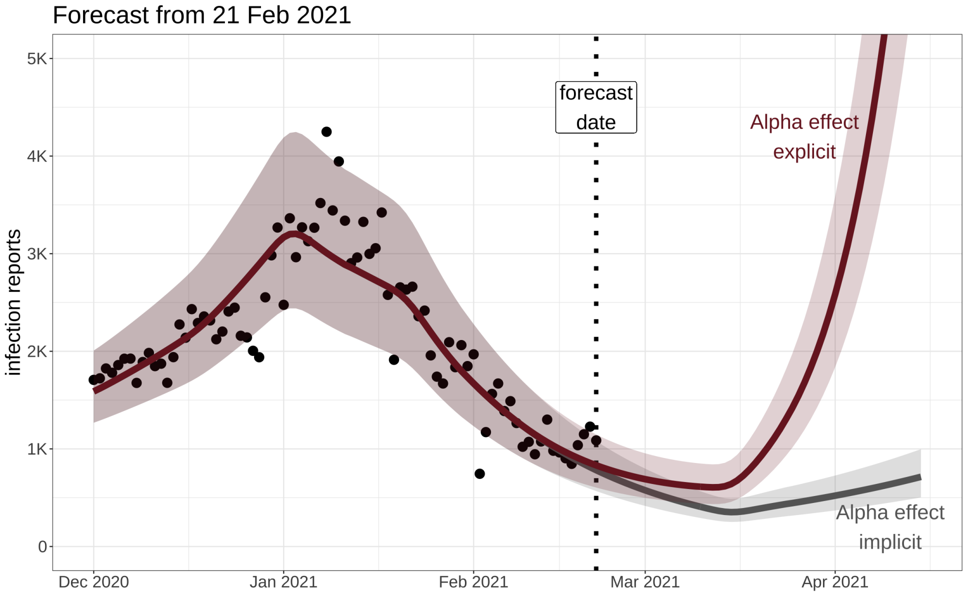
Approach:

- Expand SEIR model to include compartments for cases, deaths, hospital occupancy, *etc*
- Simultaneously fit model to all the types of data we have
- Predict the future based on various scenarios

Interpret forecasts with caution:

- Quantify uncertainties we understand (parameter estimates, observation and process noise)
- Be aware that models cannot capture all processes

Fitting and forecasting COVID-19 in Ontario



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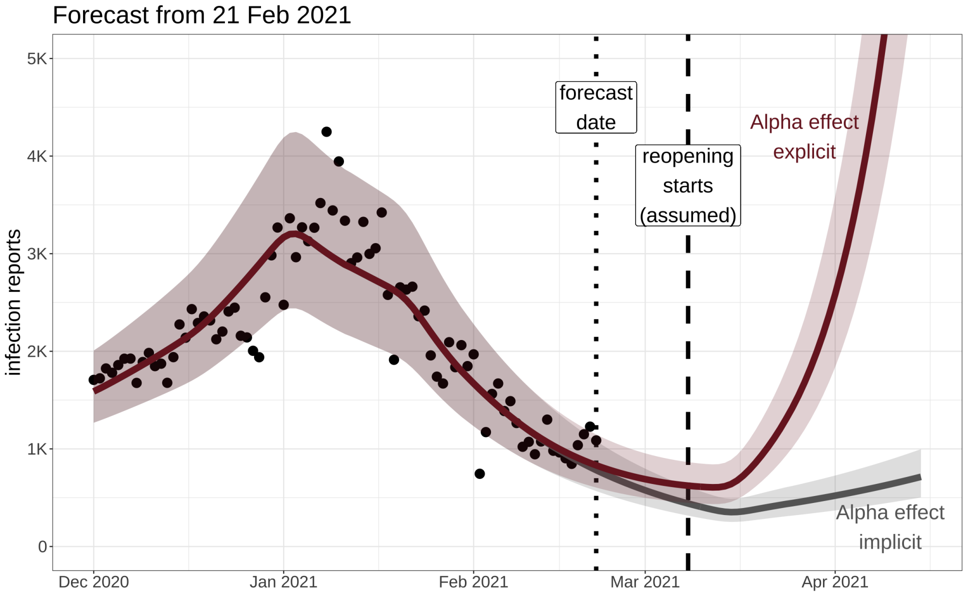

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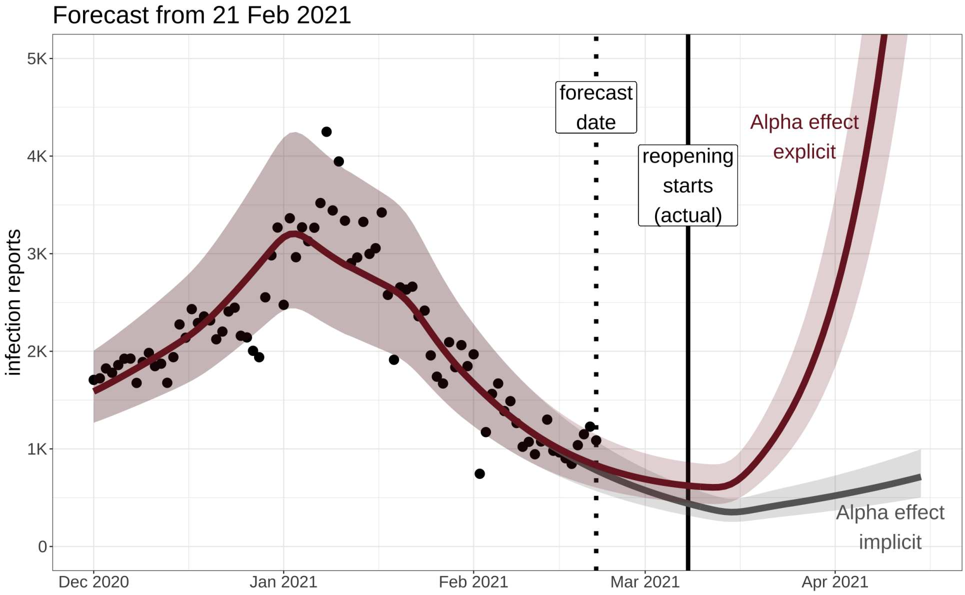

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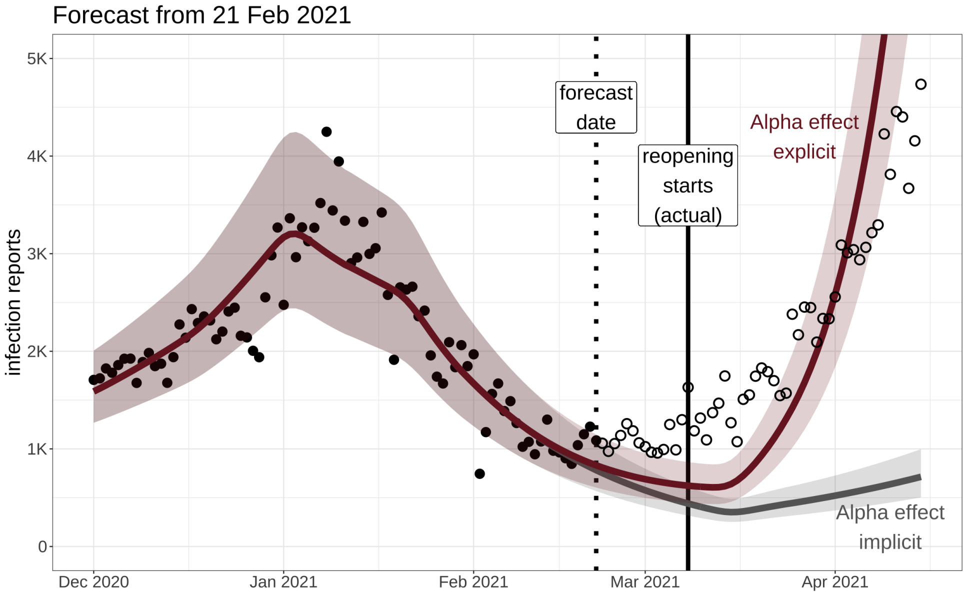

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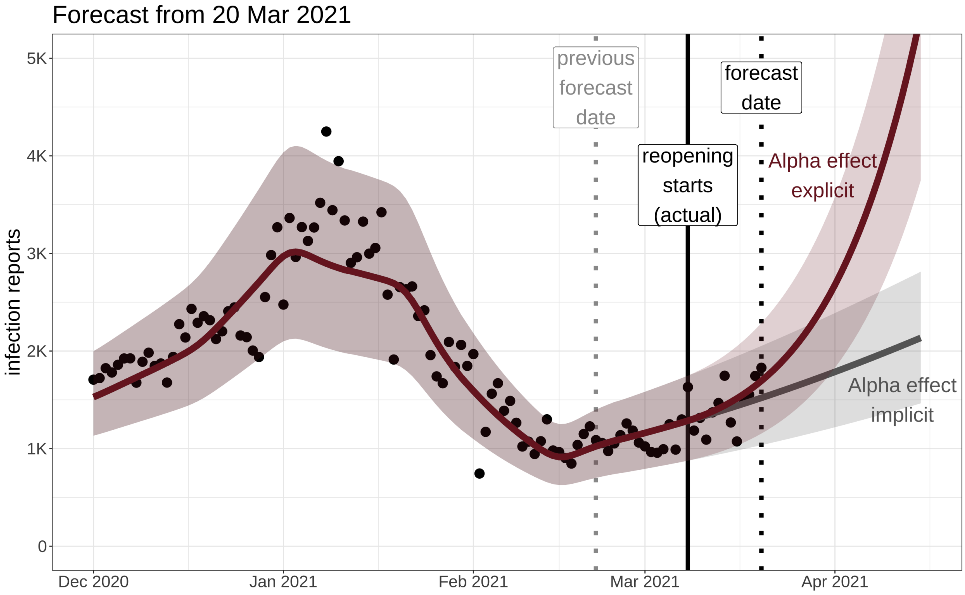

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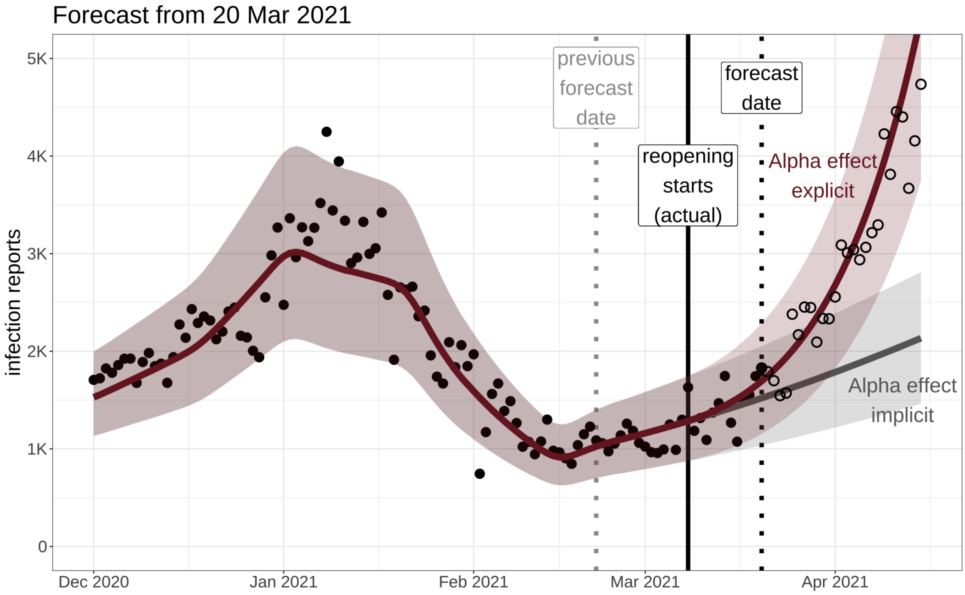

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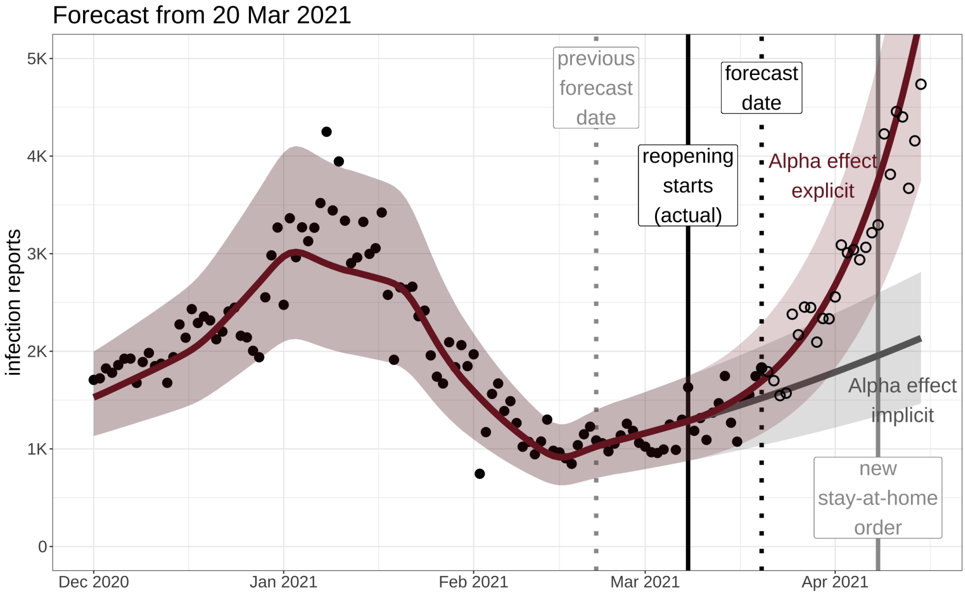

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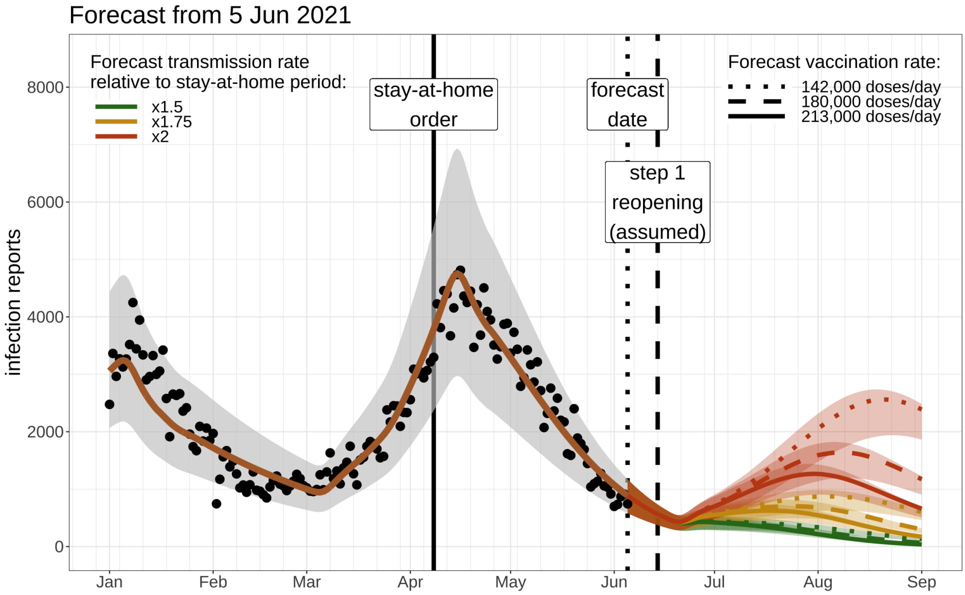

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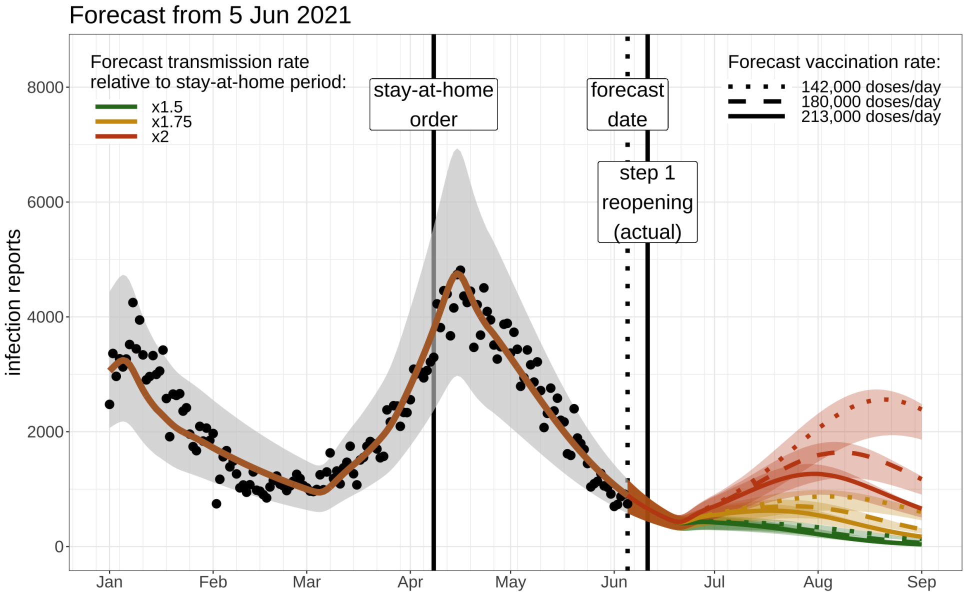

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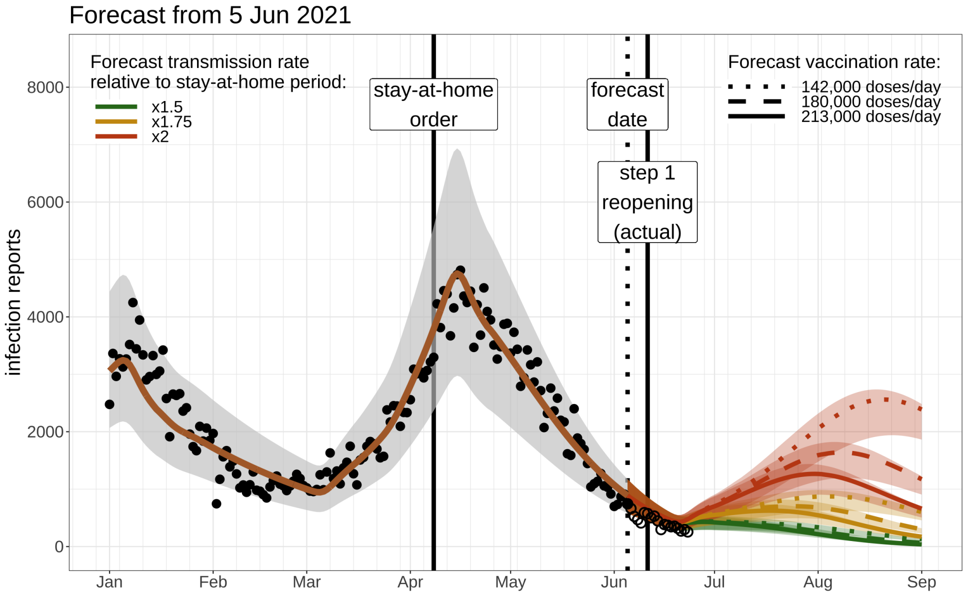

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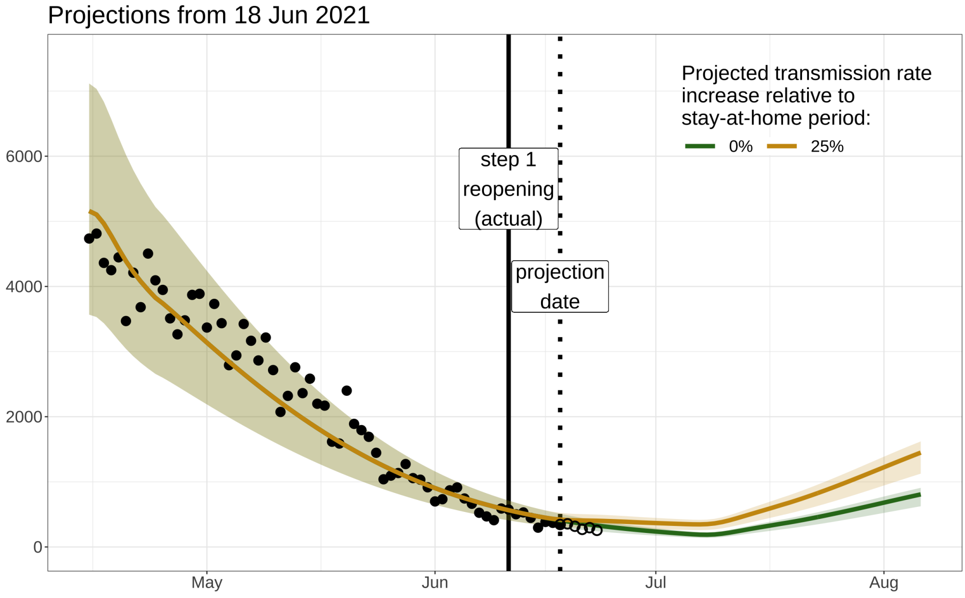

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- *University of Waterloo:* Mikael Jagan
- *Cornell University:* Irena Papst
- *Canadian Institute for Health Information (CIHI):*
  Olga Krylova

Funders:

Thanks for your interest!

https://davidearn.mcmaster.ca

https://mac-theobio.github.io/covid-19/

6 Mechanistic Modelling of Recurrent Epidemics II; $\mathcal{R}_0$

McMaster University

Mathematics and Statistics

$$\int_M d\omega = \int_{\partial M} \omega$$

Mathematics 4MB3/6MB3 Mathematical Biology

Instructor: David Earn

Lecture 6

Mechanistic Modelling of Recurrent Epidemics II

Tuesday 8 October 2024

Announcements

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- Draft Project Description Document is posted.

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- **Midterm test:**
  - *Date:* Tuesday 5 November 2024
  - *Time:* 2:30pm – 4:30pm
  - *Location:* in class, HH-102

Announcements

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  - The project is to be submitted as a paper in the style of a research article for publication. It is *not* just a big assignment.
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- **Midterm test:**
  - *Date:* Tuesday 5 November 2024
  - *Time:* 2:30pm – 4:30pm
  - *Location:* in class, HH-102
- **Assignment 4** is due the day of the midterm.

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  - *Date:* Tuesday 5 November 2024
  - *Time:* 2:30pm – 4:30pm
  - *Location:* in class, HH-102

- **Assignment 4** is due the day of the midterm.
  Due Monday 4 November 2019 before class.

Announcements

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  - *Time:* 2:30pm – 4:30pm
  - *Location:* in class, HH-102

- **Assignment 4** is due the day of the midterm.
  Due Monday 4 November 2019 before class.
  - Make sure *you personally* can do the question on calculating $\mathcal{R}_0$ on this assignment *before* the midterm test.

$\mathcal{R}_0$: biological definition

The ***basic reproduction number*** $\mathcal{R}_0$ is:

> *the expected number of secondary cases produced, in a completely susceptible population, by a typical infective individual*

e.g., Anderson and May (1991) "Infectious Diseases of Humans"

$\mathcal{R}_0$: more mathematical definition

The ***basic reproduction number*** $\mathcal{R}_0$ is:

> *the number of new infections produced by a typical infective individual in a population at a disease free equilibrium (DFE)*

van den Driessche and Watmough (2002) *Mathematical Biosciences* **180**, 29–48

$\mathcal{R}_0$: most mathematical definition

The ***basic reproduction number*** $\mathcal{R}_0$ is:

the spectral radius of the next generation operator at a disease free equilibrium (DFE)

Diekmann, Heesterbeek & Metz (1990) *J. Math. Biol.* **28**, 365–382

Definitions from matrix analysis

Definitions from matrix analysis

Definition (Spectrum of a matrix)

Let M be an $n \times n$ real (or complex) matrix. The ***spectrum of** M* is

$$\sigma(M) = \{\lambda : Mv = \lambda v \text{ for some non-zero } v \in \mathbb{C}^n\},$$

i.e., $\sigma(M)$ is the set of eigenvalues of M.

Definitions from matrix analysis

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$$\rho(M) = \max\{|\lambda| : \lambda \in \sigma(M)\}\,,$$

i.e., $\rho(M)$ is the maximum modulus of the eigenvalues of M.

Computing $\mathcal{R}_0$

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- In very simple models, $\mathcal{R}_0$ is the product of the transmission rate and the mean time in the infectious class.

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$$\mathcal{R}_0 = \beta \cdot \frac{1}{\gamma + \mu}\,.$$

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- Mathematically, the spectral radius of the next generation operator at the DFE is exactly this quantity. With this definition, it is also true that the disease persists if $\mathcal{R}_0 > 1$ and goes extinct if $\mathcal{R}_0 < 1$.

SEIR model (with vital dynamics)

$$\frac{dS}{dt} = \mu N - \frac{\beta SI}{N} - \mu S$$

$$\frac{dE}{dt} = \frac{\beta SI}{N} - \sigma E - \mu E$$

$$\frac{dI}{dt} = \sigma E - \gamma I - \mu I$$

$$\frac{dR}{dt} = \gamma I - \mu R$$

- Birth and death rate (μ)
- Transmission rate (β)
- Mean latent period ($1/\sigma$)
- Mean infectious period ($1/\gamma$)

Next generation matrix for the SEIR model

Next generation matrix for the SEIR model

- Consider flows in and out of the infected compartments

Next generation matrix for the SEIR model

- Consider flows in and out of the infected compartments, and highlight flows that correspond to new infections:

$$\frac{d}{dt}\begin{pmatrix} E \\ I \end{pmatrix} = \begin{pmatrix} \beta SI - \sigma E - \mu E \\ \sigma E - \gamma I - \mu I \end{pmatrix}$$

Next generation matrix for the SEIR model

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- $\mathcal{F} = \begin{array}{c} \text{inflow of new infecteds} \\ \text{to infected compartments} \end{array} = \begin{pmatrix} \beta SI \\ 0 \end{pmatrix}$

Next generation matrix for the SEIR model

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- Let $V =$ linearization of $\mathcal{V}$ at DFE

Next generation matrix for the SEIR model

- Consider flows in and out of the infected compartments, and highlight flows that correspond to new infections:

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- Then the ***next generation matrix*** is FV^{-1}

Next generation matrix for the SEIR model

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- Let F = linearization of $\mathcal{F}$ at DFE
- Let V = linearization of $\mathcal{V}$ at DFE
- Then the ***next generation matrix*** is FV^{-1}
- Analogous to $\beta\gamma^{-1}$ in simple case.

Interpretation of FV^{-1} as next generation matrix

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Almost verbatim from p. 33 of van den Driessche and Watmough (2002) *Mathematical Biosciences* **180**, 29–48

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- To interpret the entries of FV^{-1} and develop a meaningful definition of $\mathcal{R}_0$, consider the fate of an infected individual introduced into compartment k of a disease free population.

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- The (j, k) entry of V^{-1} is the average length of time this individual spends in compartment j during its lifetime, assuming that the population remains near the DFE and barring reinfection.

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- The (i, j) entry of F is the rate at which infected individuals in compartment j produce new infections in compartment i.
- Hence, the (i, k) entry of the product FV^{-1} is the expected number of new infections in compartment i produced by the infected individual originally introduced into compartment k.

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- The (j,k) entry of V^{-1} is the average length of time this individual spends in compartment j during its lifetime, assuming that the population remains near the DFE and barring reinfection.
- The (i,j) entry of F is the rate at which infected individuals in compartment j produce new infections in compartment i.
- Hence, the (i,k) entry of the product FV^{-1} is the expected number of new infections in compartment i produced by the infected individual originally introduced into compartment k.
- Following Diekmann et al. (1990), we call FV^{-1} the next generation matrix for the model and set

$$\mathcal{R}_0 = \rho(FV^{-1}),$$

where $\rho(A)$ denotes the spectral radius of a matrix A.

$\mathcal{R}_0$ via FV^{-1} for the SEIR model

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$$\mathcal{F} = \begin{pmatrix} \beta SI \\ 0 \end{pmatrix}$$

$\mathcal{R}_0$ via FV^{-1} for the SEIR model

$$\mathcal{F} = \begin{pmatrix} \beta S I \\ 0 \end{pmatrix} \qquad \mathcal{V} = \begin{pmatrix} \sigma E + \mu E \\ -\sigma E + \gamma I + \mu I \end{pmatrix}$$

$\mathcal{R}_0$ via FV^{-1} for the SEIR model

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$$F = \begin{pmatrix} 0 & \beta \\ 0 & 0 \end{pmatrix}$$

$\mathcal{R}_0$ via FV^{-1} for the SEIR model

$$\mathcal{F} = \begin{pmatrix} \beta S I \\ 0 \end{pmatrix} \qquad \mathcal{V} = \begin{pmatrix} \sigma E + \mu E \\ -\sigma E + \gamma I + \mu I \end{pmatrix}$$

$$F = \begin{pmatrix} 0 & \beta \\ 0 & 0 \end{pmatrix} \qquad V = \begin{pmatrix} (\sigma + \mu) & 0 \\ -\sigma & (\gamma + \mu) \end{pmatrix}$$

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$$V^{-1} = \begin{pmatrix} \frac{1}{\sigma+\mu} & 0 \\ \frac{\sigma}{(\sigma+\mu)(\gamma+\mu)} & \frac{1}{\gamma+\mu} \end{pmatrix}$$

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- Note wrt previous slide that the $(2,1)$ entry of V^{-1} is the average time an individual who enters the E compartment spends in the I compartment: only a proportion $\sigma/(\sigma + \mu)$ of such individuals make it to the I compartment, where the average time spent—by individuals who get there—is $1/(\gamma + \mu)$.

Computing $\mathcal{R}_0$ for other compartmental ODE models

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1. *$\mathcal{R}_0$ can be computed as $\rho(FV^{-1})$;*
2. *if $\mathcal{R}_0 < 1$ then the disease-free equilibrium (DFE) is locally asymptotically stable (LAS), whereas if $\mathcal{R}_0 > 1$ then there is a LAS endemic equilibrium (EE).*

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- If possible, it is best to use both methods to find an expression for $\mathcal{R}_0$, and make sure they agree.
- A completely different challenge is to estimate $\mathcal{R}_0$ for a real epidemic from data...

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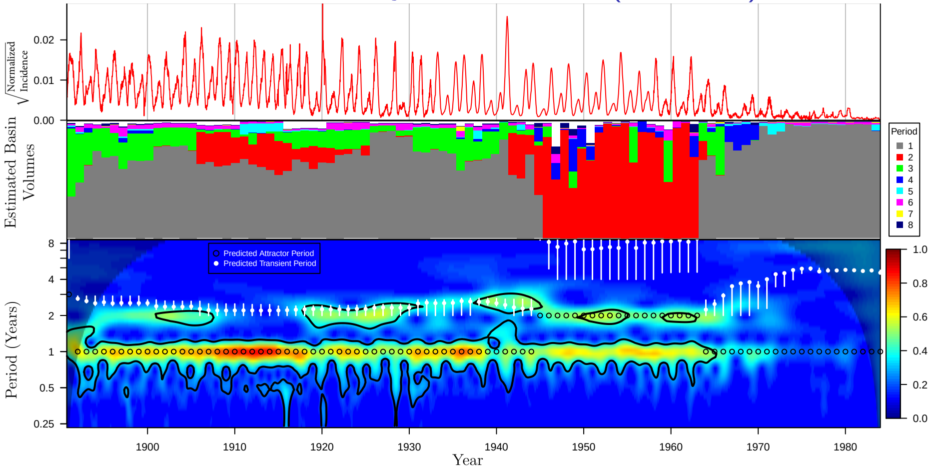
    - Solving this for β we obtain: $\beta = \dfrac{(r+\sigma+\mu)(r+\gamma+\mu)}{\sigma}$

Measles in New York City, 1891–1984 (success!)

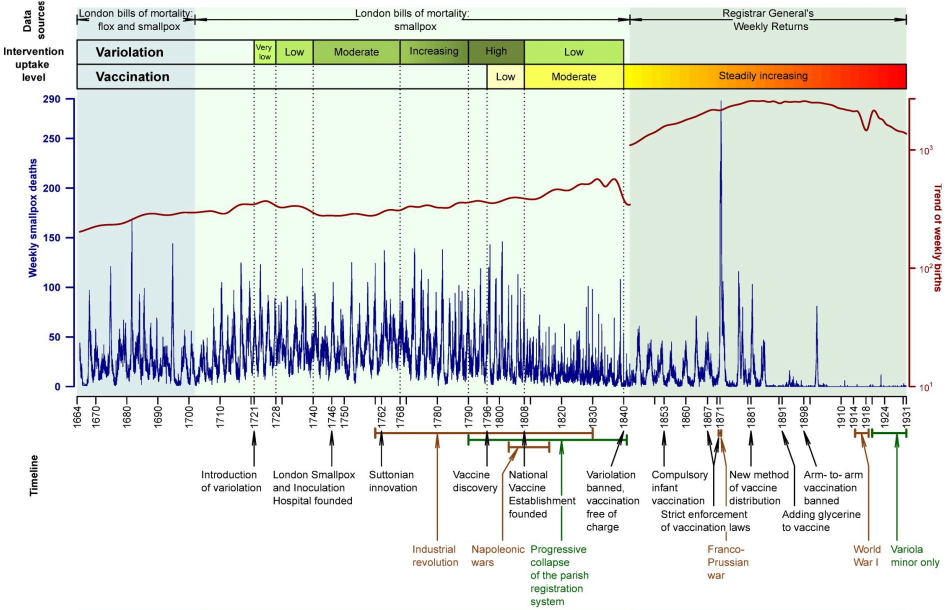


Hempel & Earn (2015) *J. R. Soc. Interface* **12**(106):20150024

- Key challenge that had to be overcome:
  changing patterns of seasonal variation in contact rates

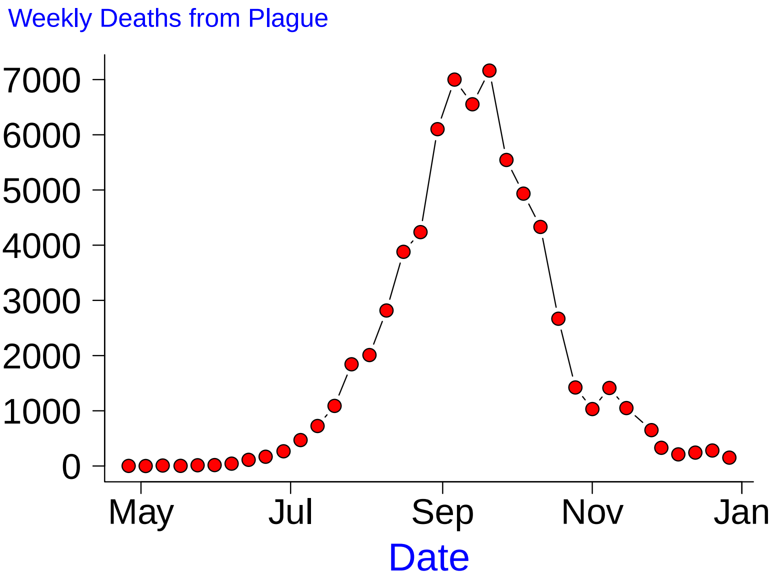
Papst & Earn (2019) *J. R. Soc. Interface* **16**:20190202
Jagan *et al.* (2020) *PLoS Comp. Biol.* **16**(9):e1008124

Smallpox in London, 1664–1930 (in progress)



Krylova & Earn (2020) *PLoS Biology* **18**(12):e3000506

The Great Plague of London, 1665



SEIR Model Fit to the Great Plague of London