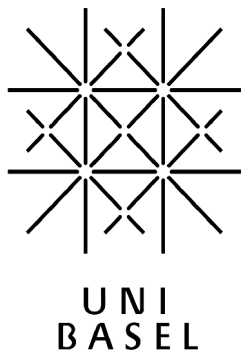
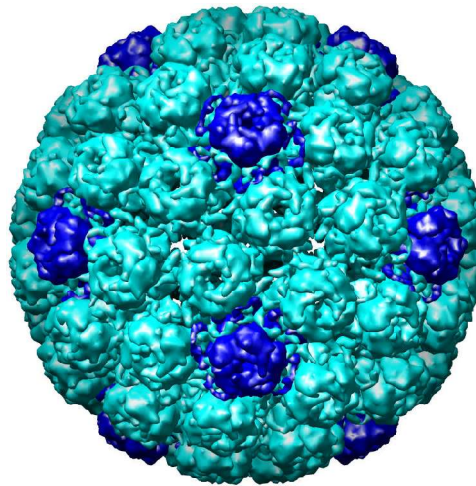
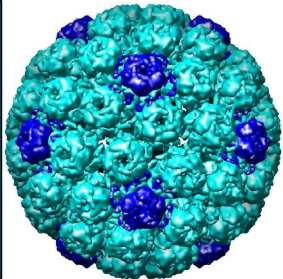


Quantification of Basic Epidemiological Characteristics: The Example of Human Polyomaviruses

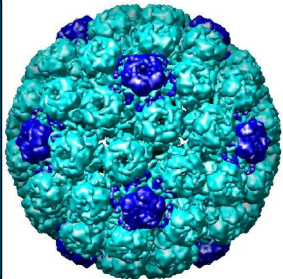


Georg A Funk
University of Basel,
Switzerland



Outline

- Learning goals
 - Epidemiological characteristics
- Results
- Polyomaviruses & their pathogenicity profiles
 - Source data, formulae & model selection
- Discussion
- Results (graphs) & summary of characteristics
 - Some limitations & context
- Summary
- Summary / take home message
- Q&A
- Q & A



Learning Goals

- Get an intuition for key epidemiol. characteristics.

- See & understand the pathway (or loop)

- > initial idea

- > data collection

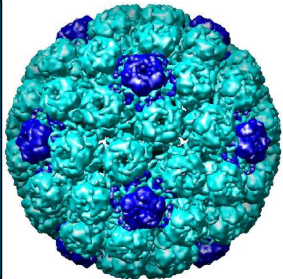
- > model construction & selection

- > parameter estimation

- > interpretation

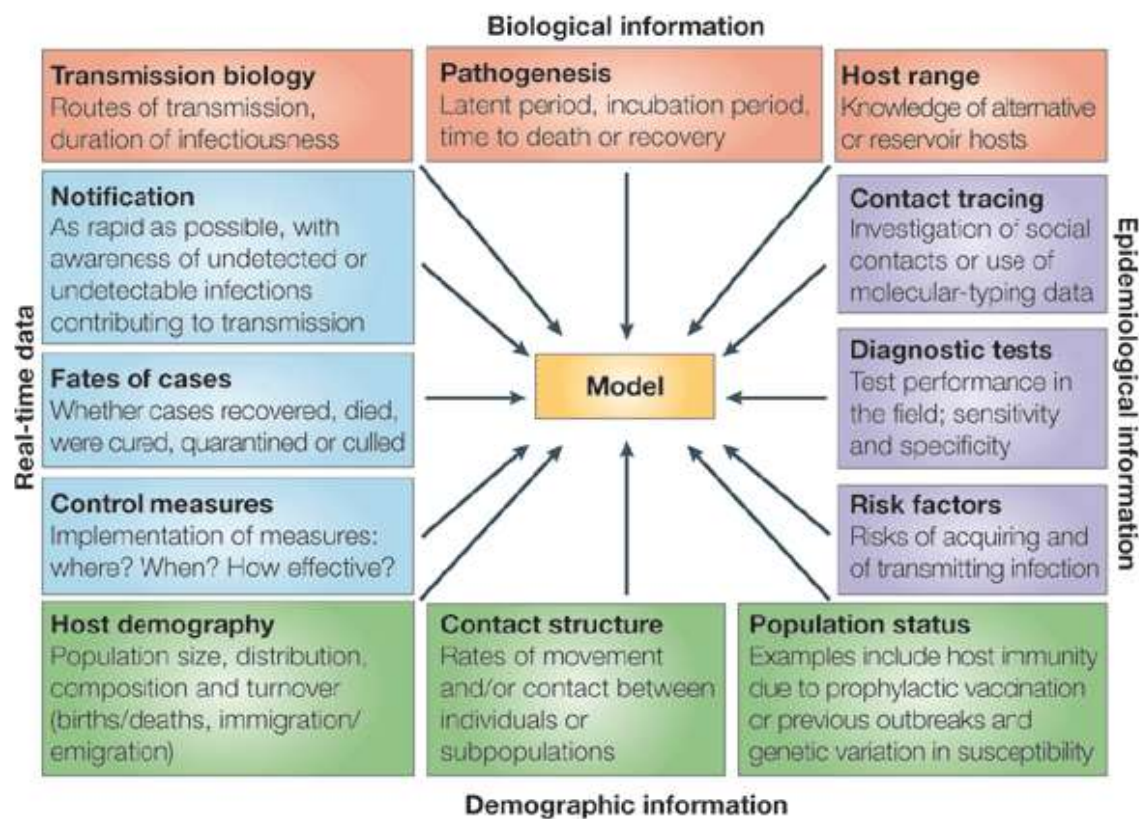
- > refinement(s)

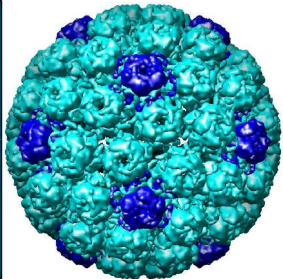
- Be able to calculate from age-stratified (sero-prevalence) data the force of infection, R_0 and H .



Epidemiology...

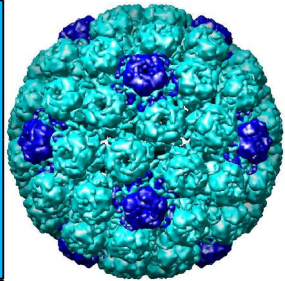
... the ecology of infectious disease(s)





Epidemiol. Characteristics

- **'Force' of infection (λ)**
(per capita rate of acquisition of infection)
- **Basic reproductive ratio (R_0)**
(secondary cases per 'index'-case)
- **Herd immunity threshold (H, p_c)**
(proportion to be immunised to control infection)
- **Further characteristics:**
 - Average age of infection (A); $A \sim \lambda^{-1}$
 - Transmission parameter (β)



The 'Force' of Infection (λ)

- Per capita rate (= 'velocity') at which susceptible individuals acquire the infection.



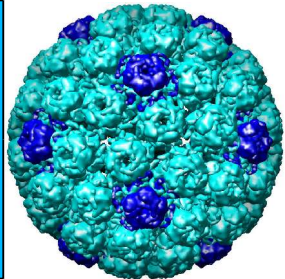
λ 'large' -> rapid



λ 'low' -> slow

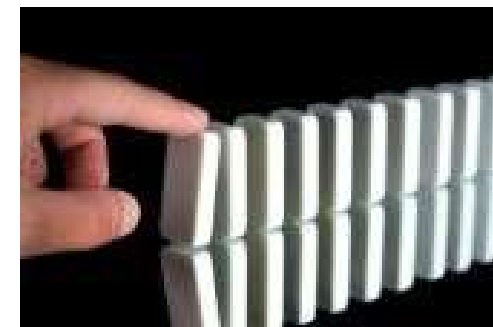


Note: λ changes as the epidemiol. circumstances change; i.e. λ is not necessarily constant over time!



Basic Reproductive Ratio (R_0)

- Expected number of secondary cases per primary case in a population where everybody except the 'index'-case is susceptible to infection.

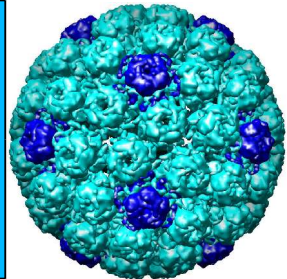


'Index'-case: $I(0) =$ one individual (see Luchsinger, p.81)

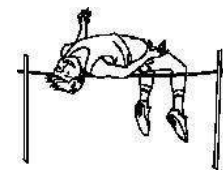
- Initial multiplication factor when considering events at the population level on a 'per generation' basis.



Generation time = serial interval = time between catching an infection and passing it on to so. else.



Herd Immunity Threshold (H)



- Proportion of the population to be immunised to reduce R_0 below unity, i.e. to control infection.

(See Smith, p.21; Luchsinger, p.82)

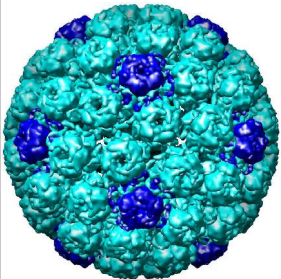
$R_0 > 1$, 'low' -> bar set low



$R_0 > 1$, 'high' -> bar set high



$R_0 < 1$ -> transient outbreak expected (see Luchsinger, p.81/82)



Basic Model & Assumptions

- **'Classical' Kermack-McKendrick (1927) SIR model**

(see Luchsinger, p.80; here with β instead of λ to avoid confusion)

Prop. Susceptibles

$$dS/dt = b - \delta S - \beta IS$$

Prop. Infecteds

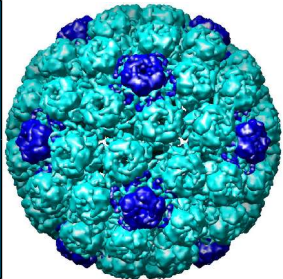
$$dI/dt = \beta IS - \mu I - (\delta + \nu)I$$

Prop. Removeds

$$dR/dt = \mu I - \delta R$$

- **Underlying assumptions:**

- population in demographic equilibrium (i.e. $b = \delta$ and $\delta \approx 0$)
- random mixing of infecteds with susceptibles
- infected individuals become immediately infectious
- negligible pathogen induced host mortality (i.e. $\nu = 0$)
- short infectious period compared with lifespan (i.e. $\mu \gg \delta$)
- removed ones cannot become infected/infectious any more



Where Are Our Quantities?

- Simplified epidemic SIR model...

Prop. Susceptibles

$$dS/dt = -\beta IS$$

Prop. Infecteds

$$dI/dt = \beta IS - \mu I = I\mu(R_0 \cdot S - 1)$$

Prop. Rremoveds

$$dR/dt = \mu I$$

'Force' of infection:

$$\lambda = \beta I$$

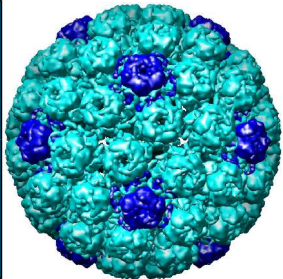
$1/\lambda \approx$ mean time an individual spends in the susceptible class

Basic reprod. ratio:

$$R_0 = \beta/\mu$$

Herd immun. thresh.:

$$H = 1 - 1/R_0 = 1 - (\mu/\beta), \text{ for } R_0 > 1$$



Derivation of H

- Goal: Proportion of infecteds I shall shrink, i.e.

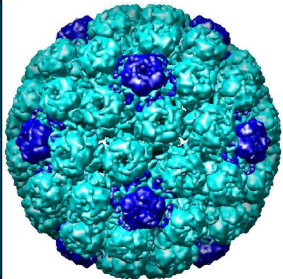
Prop. Infecteds

$$\begin{aligned}
 dI/dt &= \beta IS - \mu I \\
 &= I(\beta S - \mu) \\
 &= I(\beta(\mu/\mu)S - \mu) \\
 &= I\mu((\beta/\mu)S - 1) \\
 &= I\mu(R_0 \cdot S - 1) < 0
 \end{aligned}$$

$$\implies S_T < 1/R_0 \text{ for } I > 0, \mu > 0 \text{ and } R_0 > 1$$

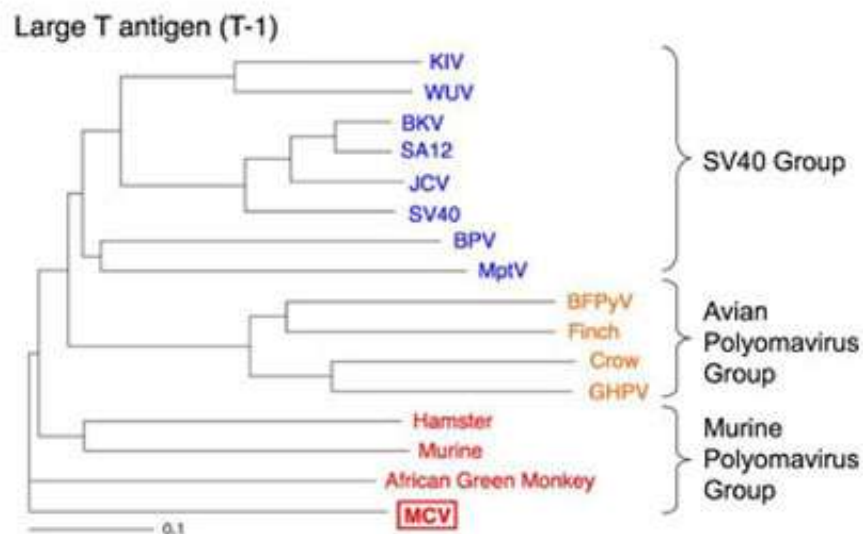
Herd immun. thresh.: $H = 1 - 1/R_0 = 1 - (\mu/\beta) \approx 1 - S_T$

Suppose $R_0 = 20 \implies S_T = 5\%$ and thus $H = 1 - 0.05 = 0.95$



Polyomaviruses

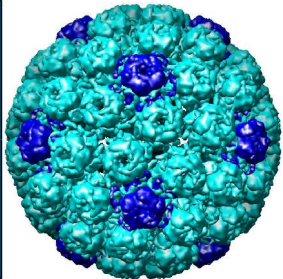
- **Small (~50 nm), non-enveloped DNA viruses**
(can infect a variety of vertebrates)



Family tree of the polyomaviruses based on the the large T antigen sequence



- **8 'human related' polyomaviruses known**
(5 were discovered in the past 4 years!)



Why Interesting to Study?

- **Ubiquitous virus(es)**

- No vaccines -> host-pathogen system in **endemic** equilibrium; i.e. $I(t) > 0$ for extended periods of time

- **Disease(s) only when **immunity** is compromised**

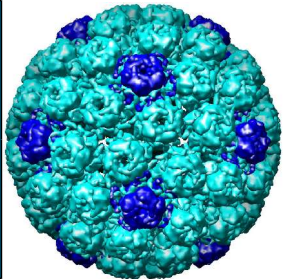
- HIV / AIDS
- Transplantation

- **Not much is known...**

... in particular reg. epidemiol. characteristics

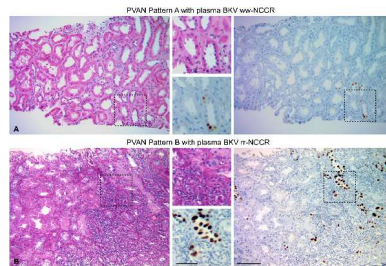
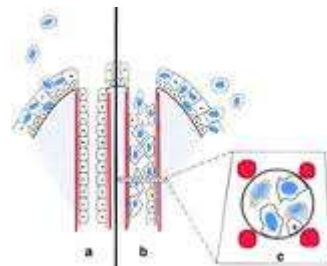
- **Improve clinico-epidemiological knowledge**

(help to device approaches for better protecting patients at risk)

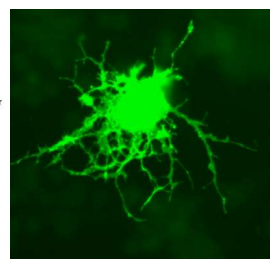
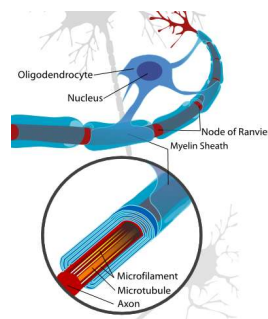


Pathogenicity Profiles

- BKV -> Nephropathy



- JCV -> PML

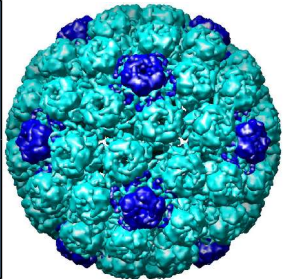


(demyelating brain cells)

- MCV -> Merkel Cell Carcinoma



- Other polyomaviruses respiratory illnesses?
(SV40, KIV, WUV, TSV) **transforming capacity**

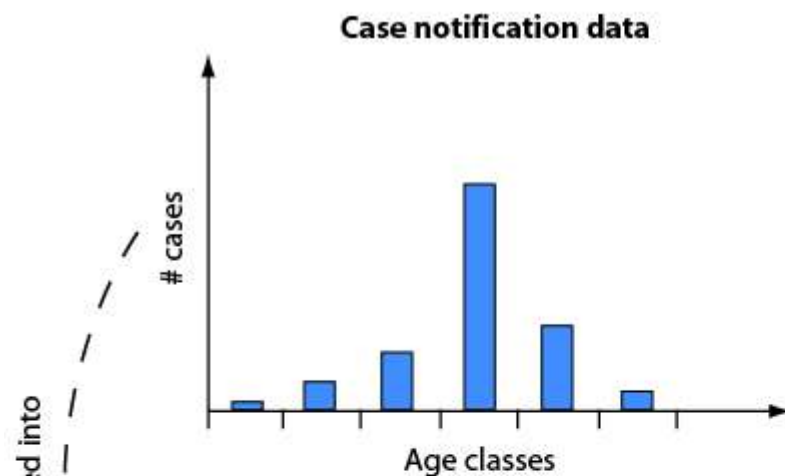


Types of Data

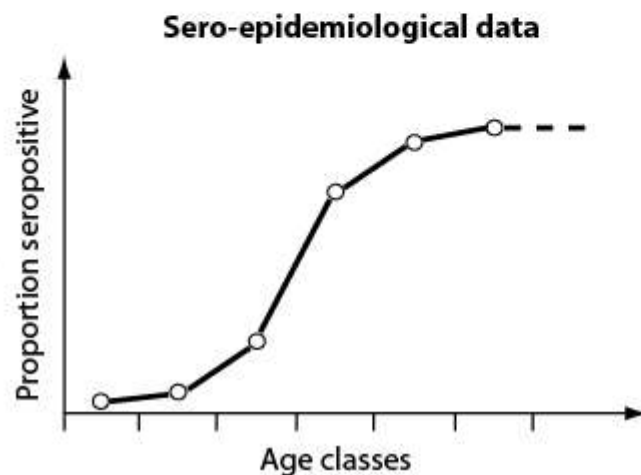
real-time,
ongoing

retrospective

Raw data



to be transformed into

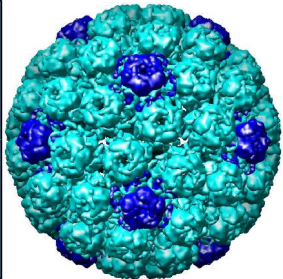


Limitations:

- representative sample
- fine age stratification
- no underreporting

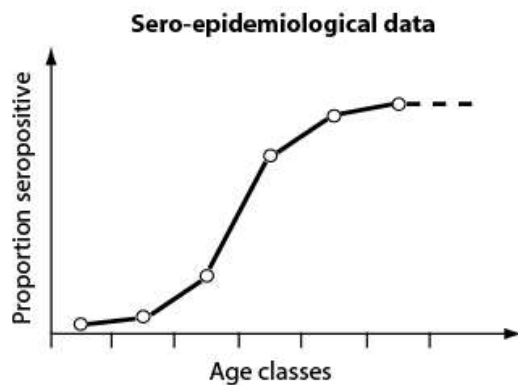
Limitations:

- representative sample
- fine age stratification
- sensitive and specific assay



Interrelation of Characteristics

Raw data



Limitations:

- fine age stratification
- representative sample
- sensitive and specific assay

Key quantity

Force of infection, λ
per capita rate of acquisition
of infection

Assumption:

- infection is at its
endemic equilibrium

Derivatives

Basic reproductive ratio, R_0
secondary cases per (index-) case
if λ_c is supposed to be fix over life

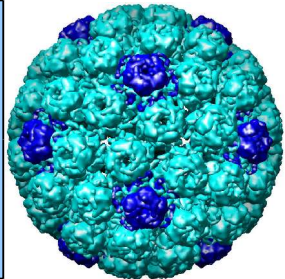
← Life expectancy, L

Herd immunity threshold, H
proportion of the population to be
immunised to control infection

← 100% efficacy of
antiviral measures

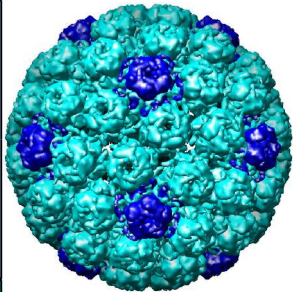
Invasion criterion & cross-immunity
threshold an invading pathogen has to
overcome in face of resident pathogen

← Degree of cross-
immunity, ε



Source Data

- **Age-stratified sero-epidemiological surveys**
 - ideally **longitudinal** ('follow' an individual; inexistent), here **cross-sectional** (all age-strata sampled simultaneously)
 - sensitive and specific assays (HIA, ELISA)
 - at regular time intervals
 - a large unbiased sample of the population
- **PubMed® search: 11 studies providing 22 data sets**
(7 BKV, 6 JCV, 2 SV40, 1 LPV, 2 KIV, 2 WUV, 2 MCV)



Data Extraction: Example

BRITISH MEDICAL JOURNAL 13 JANUARY 1973

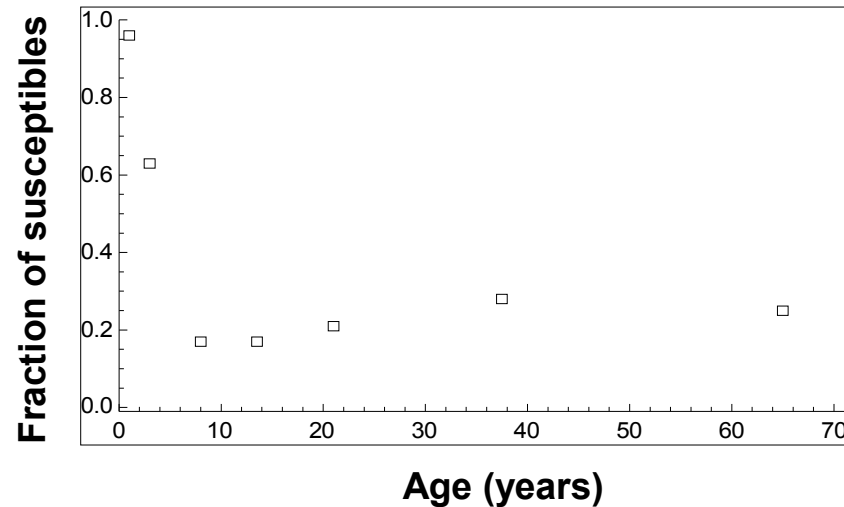
Prevalence in England of Antibody to Human Polyomavirus (B.K.)

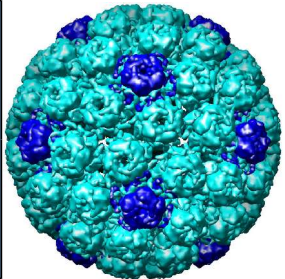
SYLVIA D. GARDNER

TABLE II—Haemagglutination-inhibiting Antibody to B.K. Virus in Human Sera

Age Group	No. of Sera Tested	No. of Sera with Antibody	Percentage with Antibody	Range of Titres	Percentage Sera with Titres 2,560 or Greater
0-3 months	36	24	67	40-5,120	35
4-11 "	54	2	4	40-160	0
1-5 years	46	17	37	40-5,120	11
Primary schoolchildren (4-6 years)	48	35	73	40-5,120	51
6-10 years	52	43	83	160- $\geq 20,480$	35
11-17 "	40	33	83	40- $\geq 20,480$	36
18-25 "	34	27	79	40-2,560	4
26-50 "	46	33	72	40-10,240	20
>50 "	53	40	75	40- $\geq 20,480$	8
Total	409	254	62		

Polyomavirus type, reference, region & assay	Source data			Estimate
	Age class	% sero-preval.	Sample size	FoI _A (1/y)
BKV				
Gardner 1973	0-1	4	54	NA
United Kingdom	1-5	37	46	0.084
HIA (≥ 40)	6-10	83	52	0.262
	11-17	83	40	0
	18-25	79	34	-0.026
	26-50	72	46	-0.012
	≥ 50	75	53	NA





Epidemiol. Characteristics

- **'Force' of infection (λ) in interval $i, i+1$**

$$\lambda_i = -\ln[(1 - p_{i+1}) / (1 - p_i)]$$

p_i -> proportion of those who have experienced infection at age i

(Anderson & May, 1983, Appendix 2, Eqs. 2.2 & 2.9; and 1985, Eq. 58)

- **Basic reproductive ratio (R_0)**

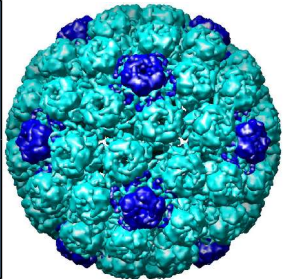
$$R_0 = (\lambda_c \cdot L) / (1 - \text{Exp}(-\lambda_c \cdot L))$$

L -> life expectancy = 80 years, type I mortality;

λ_c -> 'childhood' force of infection

- **Herd immunity threshold (H, p_c)**

$$H = 1 - 1 / R_0$$



Model Selection & Fitting

- Competing candidate models (4-5) ranked by Akaike's information criterion

$$AIC_c = 2 \cdot p + n \cdot [\ln(2 \cdot \pi \cdot RSS / n) + 1] + 2 \cdot p \cdot (p + 1) / (n - p - 1)$$

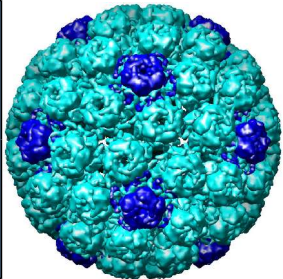
penalty for
model complexity

goodness of fit

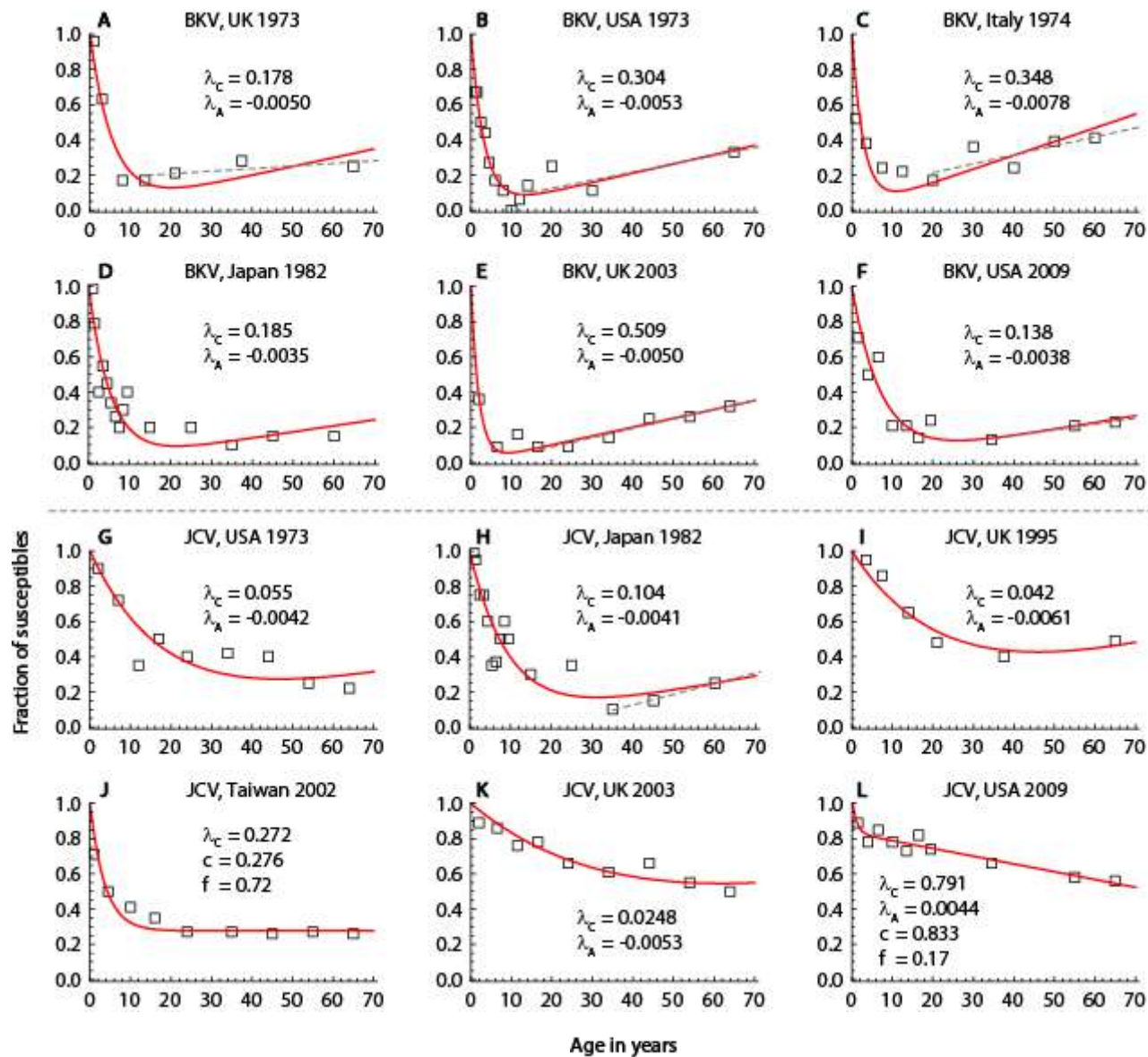
correction for
small sample size

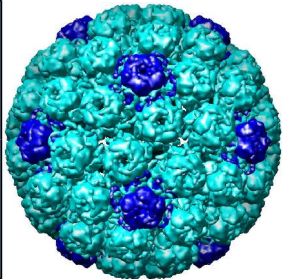
RSS = residual sum of squares; p = number of parameters; n = sample size

- Models with lowest AIC_c score are shown (fitted by nonlinear least squares)

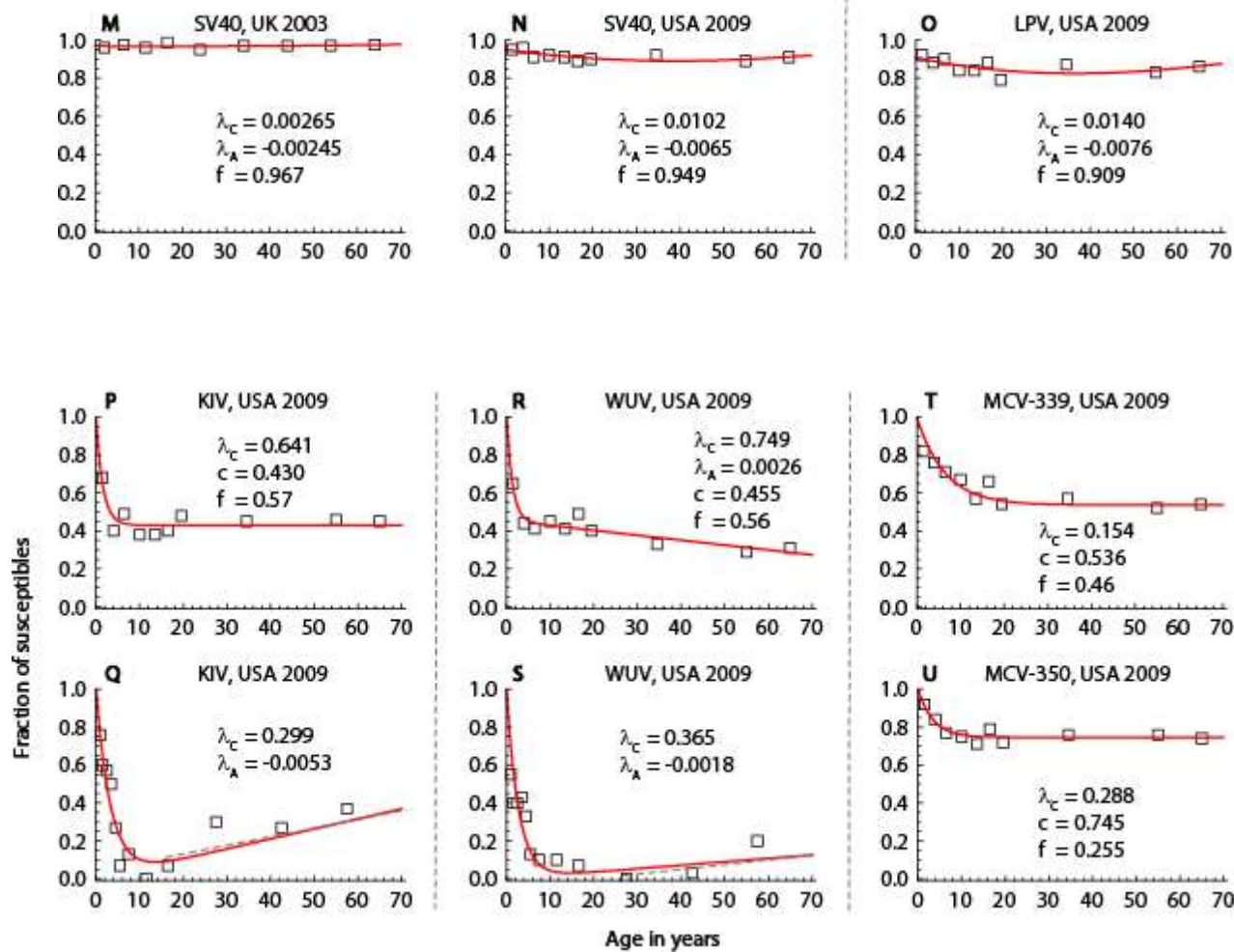


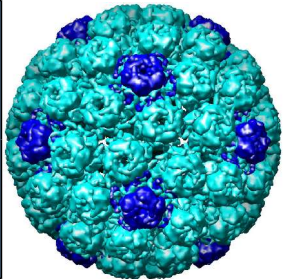
Polyomaviruses BKV & JCV





SV40, KIV, WUV & MCV



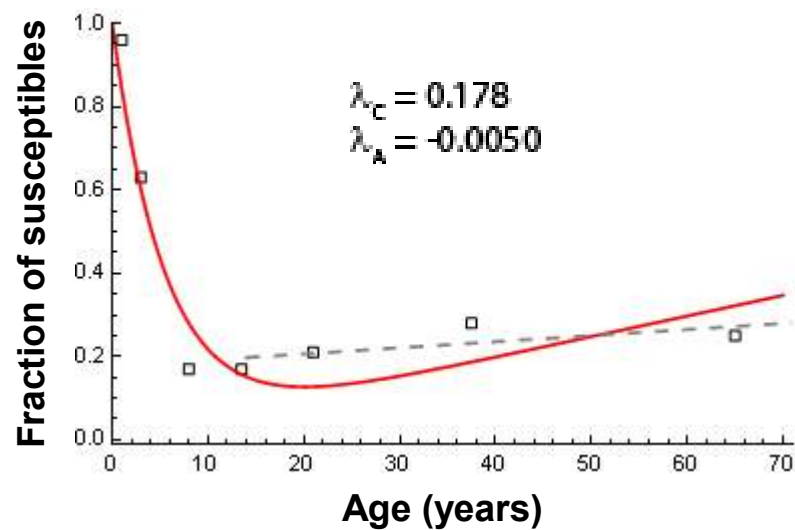


Characteristics: Example

BRITISH MEDICAL JOURNAL 13 JANUARY 1973

Prevalence in England of Antibody to Human Polyomavirus (B.K.)

SYLVIA D. GARDNER



Study type: BKV
 Author: Gardner, 1973

Model prob.: 0.93

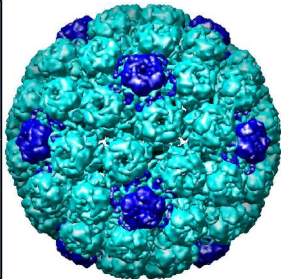
λ_c (1/y): 0.178 (95% CI: 0.094-0.263)

R_0 : 14.3 (95% CI: 7.5-21)

$H_{L=80}$ (in %): 93 (95% CI: 87-95)

Sensitivity
 $H_{L=70}$ (in %): 92

delta H: -1.08%



Summary of Characteristics

Virus Type	Study (author, year)	Model prob.	Fol (1/y)	Lower 95% CI	Upper 95% CI	R0	Lower 95% CI	Upper 95% CI	H in % (L=80)	Lower 95% CI	Upper 95% CI	H in % (L=70)	% change $H_{L=70}$ vs $H_{L=80}$
BKV	Gardner 1973	0.93	0.178	0.094	0.263	14.3	7.5	21.0	93	87	95	92	-1.08
	Shah 1973	0.85	0.304	0.248	0.359	24.3	19.9	28.7	96	95	97	95	-0.61
	Portolani 1974	0.59	0.348	0.154	0.543	27.9	12.3	43.4	96	92	98	96	-0.53
	Taguchi 1982	0.45	0.185	0.140	0.230	14.8	11.2	18.4	93	91	95	92	-1.03
	Tavis 1990	0.72	0.640	0.456	0.823	51.2	36.5	65.8	98	97	98	98	-0.28
	Knowles 2003	0.99	0.509	0.373	0.645	40.7	29.9	51.6	98	97	98	97	-0.36
	Kean 2009	0.89	0.138	0.098	0.178	11.1	7.8	14.3	91	87	93	90	-1.42
JCV	Padgett 1973	0.60	0.055	0.034	0.076	4.4	2.9	6.1	77	66	84	74	-3.85
	Taguchi 1982	0.72	0.104	0.076	0.131	8.3	6.1	10.5	88	84	90	86	-1.95
	Gardner 1995	0.84	0.042	0.025	0.058	3.5	2.3	4.7	71	57	79	68	-4.9
	Chang 2002	0.99	0.272	0.125	0.420	21.8	10.0	33.6	95	90	97	95	-0.69
	Knowles 2003	0.79	0.025	0.015	0.034	2.3	1.7	2.9	57	42	66	53	-7.04
	Kean 2009	0.94	0.791	-0.570	2.152	63.3	0.0	172.1	98	0	99	98	-0.23
SV40	Knowles 2003	0.86	0.003	-0.010	0.015	1.1	0.7	1.7	10	0	42	9	-11.75
	Kean 2009	0.77	0.010	0.004	0.017	1.5	1.2	1.8	32	13	45	29	-9.84
LPV	Kean 2009	0.90	0.014	0.003	0.025	1.7	1.1	2.3	40	11	57	36	-9.02
KIV	Kean 2009	0.89	0.641	0.297	0.985	51.3	23.8	78.8	98	96	99	98	-0.28
	Nguyen 2009	0.98	0.299	0.222	0.376	23.9	17.8	30.1	96	94	97	95	-0.62
WUV	Kean 2009	0.92	0.749	0.342	1.155	59.9	27.3	92.4	98	96	99	98	-0.24
	Nguyen 2009	0.49	0.365	0.261	0.468	29.2	20.9	37.5	97	95	97	96	-0.51
MCV-339	Kean 2009	0.95	0.154	0.066	0.242	12.3	5.3	19.4	92	81	95	91	-1.26
MCV-350	Kean 2009	0.94	0.288	0.130	0.445	23.0	10.4	35.6	96	90	97	95	-0.65

Legend:

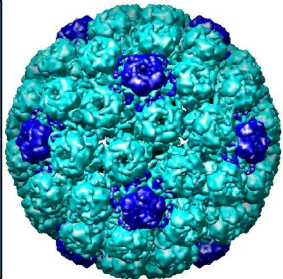
Model prob.: probability (Akaike weight) of the respective best fitting model.

Fol: force of infection (parameter lamda(c)) reported in each panel of Figure 2.

R0: estimated basic reproductive ratio obtained by assuming a life expectancy of L=80 years.

H: herd immunity thresholds H for assumed life expectancies L of 80 or 70 years, respectively.

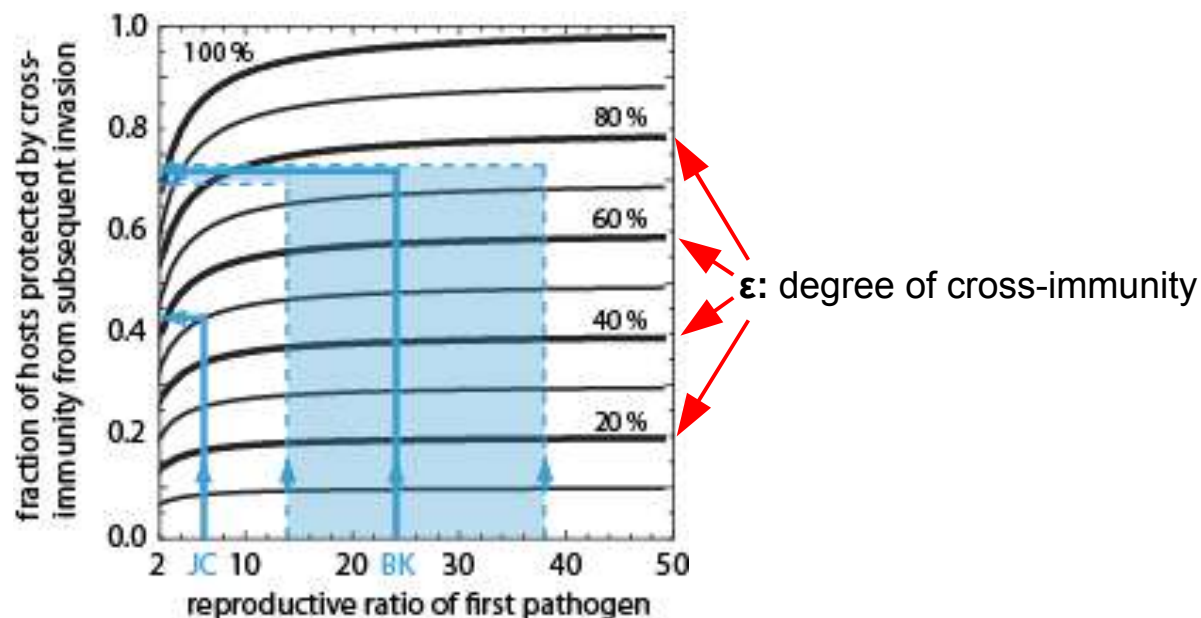
% change: reduction of H in % if the life expectancy was assumed to be 70 years instead of 80 years.



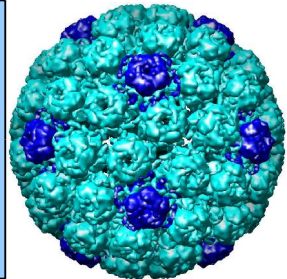
Cross-Immunity?

- Expectation if cross-immunity would exist between BKV or JCV and SV40

Invasion criterion: $R_0^{INV} [1 - \epsilon (1 - 1 / R_0^{EST})] > 1$

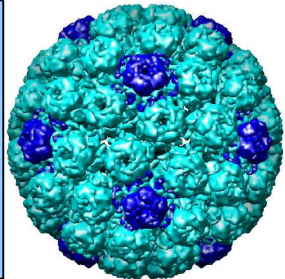


- SV40 does not surpass the invasion threshold!



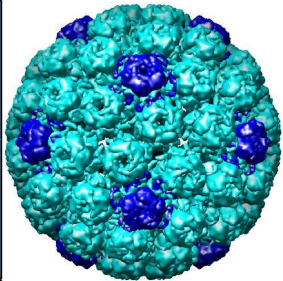
Some Limitations

- **Quality of (source) data!**
 - Actuality (2/3 of data after year 2000)
 - Accuracy (endemic infection, lasting sero-conversion)
 - Origin (only peer-reviewed studies, critically appraised)
- **Sero-reversion of ~5% per decade during adulthood**
($dI/dt < 0$ due to low S ?; any balance between sero-conversion and sero-reversion? ==> **longitudinal studies**)
- **Does cross-immunity hinder SV40 from invasion?**
(**neutralizing** or binding antibodies?
cellular immunity is totally missing)



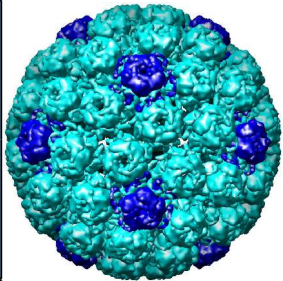
Broader Context

- Lack of **extended** protection by maternal antibodies
- **Rapid acquisition of polyomaviruses** at an age when toddlers have increasing numbers of **social contacts**
median age: 5-7 years → family (-), companions(+)
median FoI: $\sim 0.3/y$ → compares well with **measles**
- **Ten times faster than acquisition of cytomegalovirus**
- **Acquisition during adulthood ~ 200 -fold slower as during childhood (reactivations?)**
- **Protection of immunocompromised patients must be both highly efficient and well targeted (infants may be 'vectors')**



Summary

- First quantitative study describing polyomavirus circulation, vital to inform virus control strategies.
- Complements recent reports proposing the development of candidate vaccines, e.g. against MCV.
- Conform acquisition profiles of BKV across space (Asia, Europe, USA) and time (1973-2009).
- Sero-conversion during childhood driven by a median force of infection of $\sim 0.3/\text{y}$ ($R_0 \approx 24$).
- Herd immunity thresholds of BKV, KIV, WUV or MCV are comparable with those of measles, i.e. high!
- Antibodies against most polyomaviruses are on the wane any time (albeit slowly, sero-reversion rate $\sim 0.005/\text{y}$).

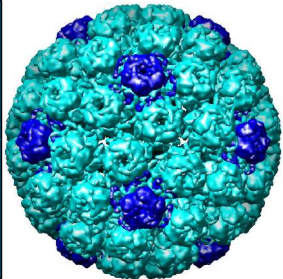


Thank You!



"I think it's a Pig virus..."

Questions?



Endemic SIR Model

- Considering demographic turnover, etc., leads to

Prop. Susceptibles $dS/dt = b - \delta S - \beta IS$

Prop. Infecteds $dI/dt = \beta IS - \delta I - \mu I$

Prop. Rremoveds $dR/dt = \mu I - \delta R$

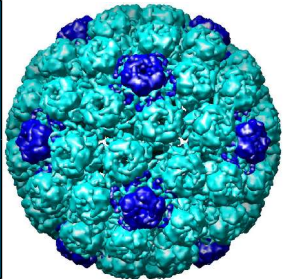
'Force' of infection: $\lambda = \beta I^*$, with $I^* = (\delta/\beta)(R_0 - 1)$

$1/\lambda \approx$ mean time an individual spends in the susceptible class

\approx average age of infection, denoted A , with $A \approx 1/(\delta(R_0 - 1))$

Basic reprod. ratio: $R_0 = S_0 \cdot \beta / (\delta + \mu)$, with $S_0 = b/\delta$

Herd immun. thresh.: $H = 1 - 1/R_0$



Derivation of λ_i

(see Anderson & May, 1983, Appendix 2, Eqs. 2.2 & 2.9; and 1985, Eq. 58)

Prop. Susceptibles at age i

- constant λ $S(i) = \exp[-\lambda i]$ Eq. 2.1

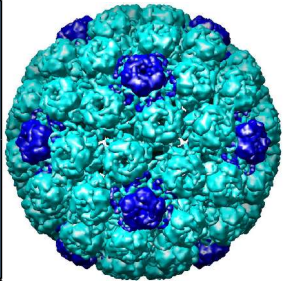
- age dependent λ $S(i) = \exp[-\int_0^i \lambda(x) dx]$ Eq. 2.2

λ_i in interval $i+\Delta i$, with Δi relatively small

$$i+\frac{1}{2}\Delta i = -\ln[S(i+\Delta i)/S(i)] / \Delta i \quad \text{Eq. 2.9}$$

by means of Eq. 2.2 where $i+\frac{1}{2}\Delta i$ is given as by Eq. 2.9, and observing that $S(i+\Delta i) = (1-p_{i+\Delta i})$ we obtain

$$\lambda_i = -\ln[(1-p_{i+\Delta i})/(1-p_i)] \quad \text{Eq. 58}$$



Why Modelling?

- **Modelling allows to...**

- identify gaps in our knowledge
- take a fresh look at old data or phenomena
- generate new hypotheses
- explore them in silico before performing costly & time consuming experiments
- improve clinical decisions
- ...

and it makes fun!