Co-infections by non-interacting pathogens are not independent and require new tests of interaction

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Joint work with *Nik Cunniffe, Linda Allen et al.*

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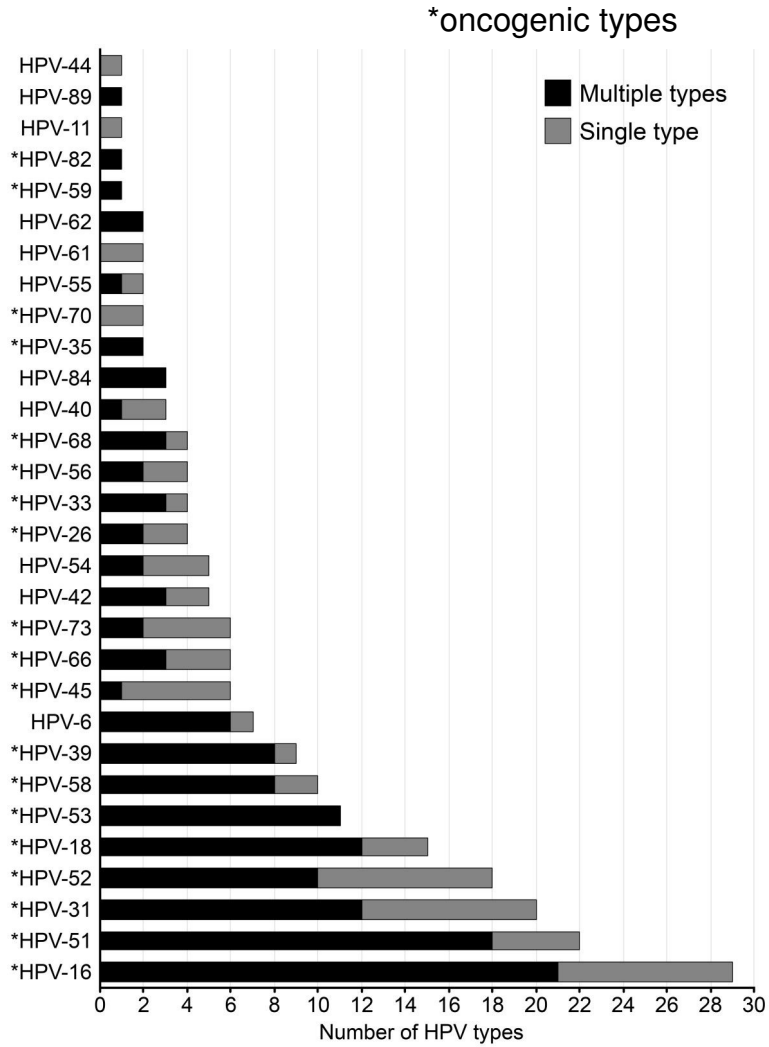
CO-INFECTIONS AND INTERACTIONS

HPV AS AN EXAMPLE FOR SIMILAR PATHOGENS

Co-infection is the simultaneous infection of one host by multiple pathogen species or strains or clones or types, from now on **pathogens**.

Human papillomavirus

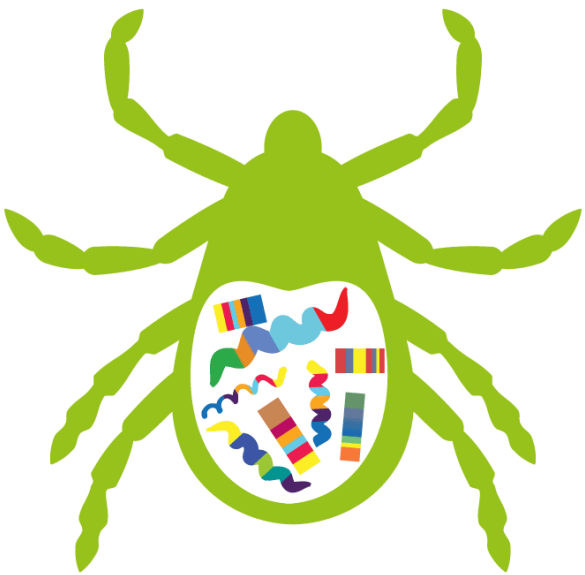
- many HPV types
- high-risk (oncogenic) types
- co-infections are common
- within-host **interactions** between types is debated
- vaccinating against one type may impact other types

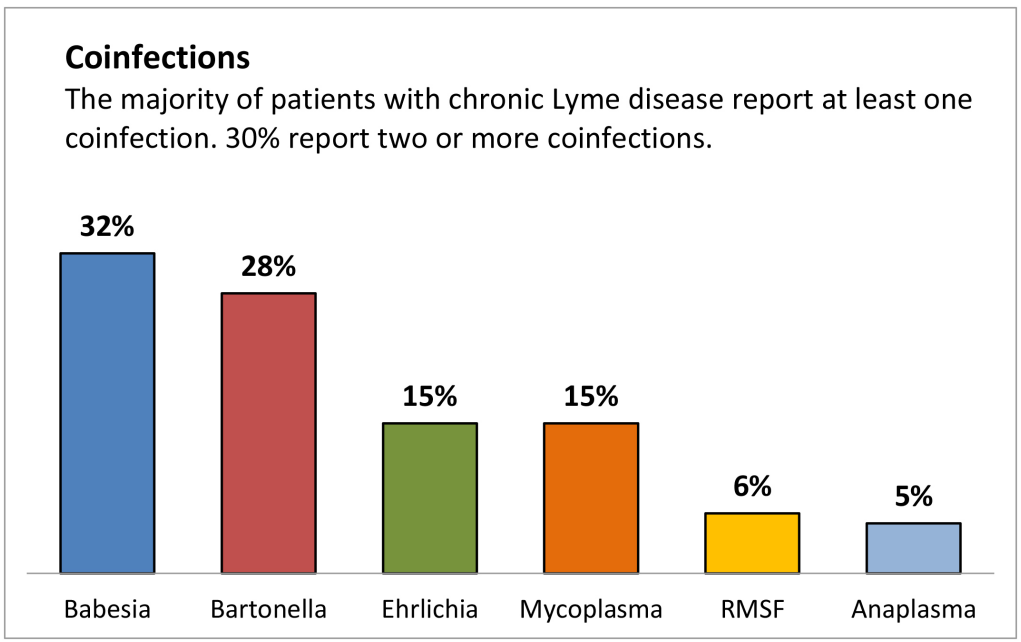


CO-INFECTIONS AND INTERACTIONS

LYME DISEASE AS AN EXAMPLE FOR DISTINCT PATHOGENS

Ticks are “toxic soup” and coinfections are the rule, including babesiosis, anaplasmosis, Rocky Mountain spotted fever, *etc.*





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CO-INFECTIONS AND INTERACTIONS

MALARIA AS AN EXAMPLE OF TESTING FOR INTERACTIONS

Forbes (1907) and Cohen (1973) introduced

$S =$ ratio of observed coinfections to the number expected if pathogens were statistically independent

If

$S > 1$ pathogens positively associated

$S = 1$ no significant association

$S < 1$ pathogens negatively associated

Statistical associations are taken as a signal of **biological interactions**

The idea of studying the ratio s of the number of observed joint occurrences of species to the number expected if species were independent, though proposed independently for this study, dates back in ecology at least to Forbes (1907).

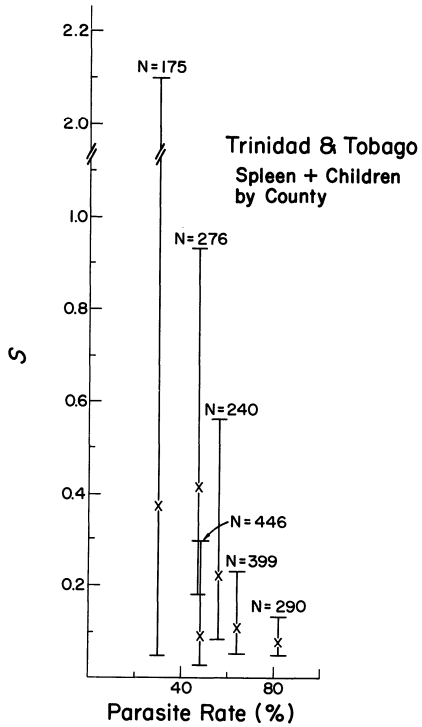


FIG. 1. MALARIAL INFECTIONS IN 6 COUNTIES IN TRINIDAD AND TOBAGO

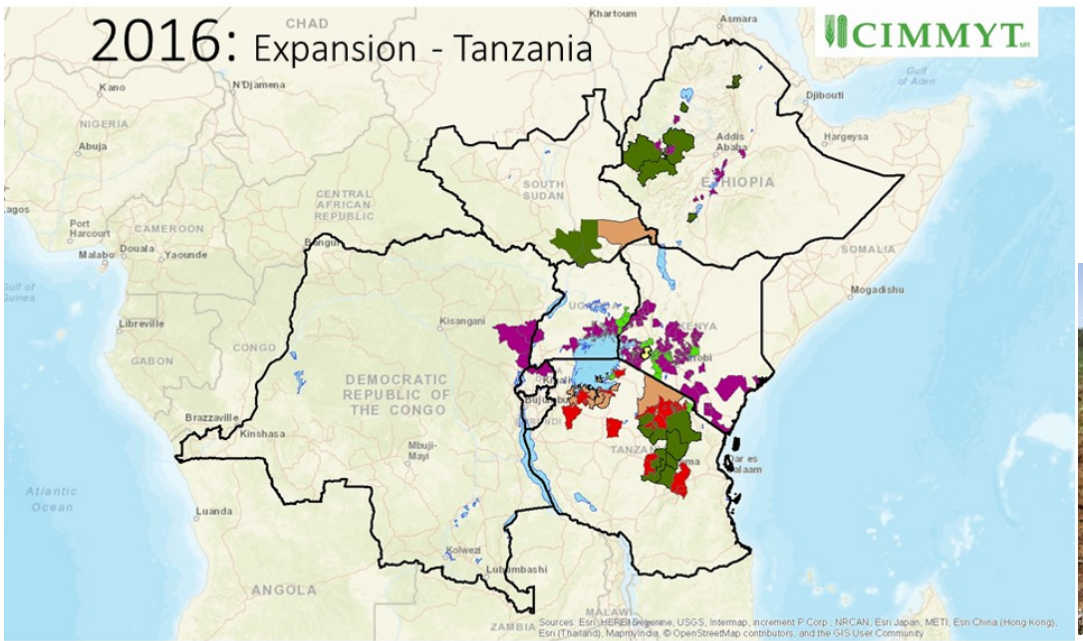
Estimates (x) and 99% confidence intervals (vertical bars) of s as a function of parasite rate (fraction of the population with malarial infection). See Table 1, based on Downs, Gillette, and Shannon (1943). In this and all of the following figures, s is the ratio of the number of mixed infections observed to the number that would have been expected if there were no interactions among the parasite species.

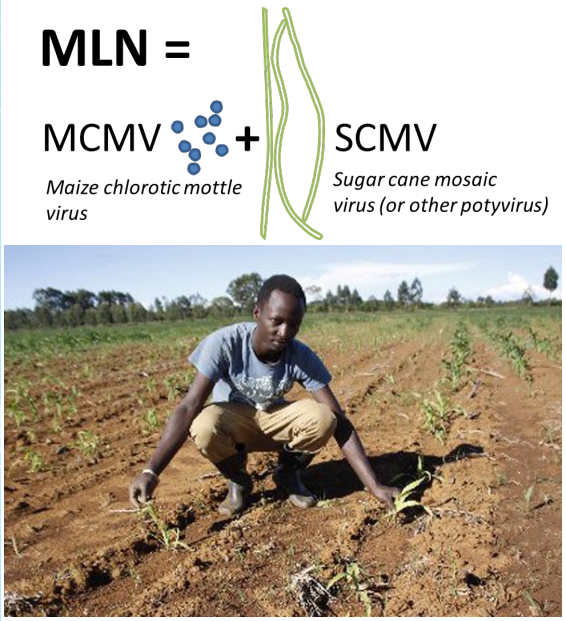
How did I came to this topic

Maize Lethal Necrosis as a motivating example

MLN is a disease caused by co-infections by two viruses

MLN Distribution and Spread 2011- 2016





Data Sources: KALRO, KEPHIS, FAO, EIAR, NARO, RAB, MARI, UCG, IITA, CIMMYT

NIMBioS Working Group “Multiscale Vectored Plant Viruses” focused on MLN

CO-INFECTION MODEL TO INFORM CONTROL OF MLN

HILKER ET AL (2017) PHYTOPATHOLOGY

- Analyzed a (very) simple model of MLN
- Assumed the two viruses do not interact (within the season)
- **Multiplicative prevalence** in field data support this (strong) assumption
- Multiplicative prevalence means **statistical independence**:

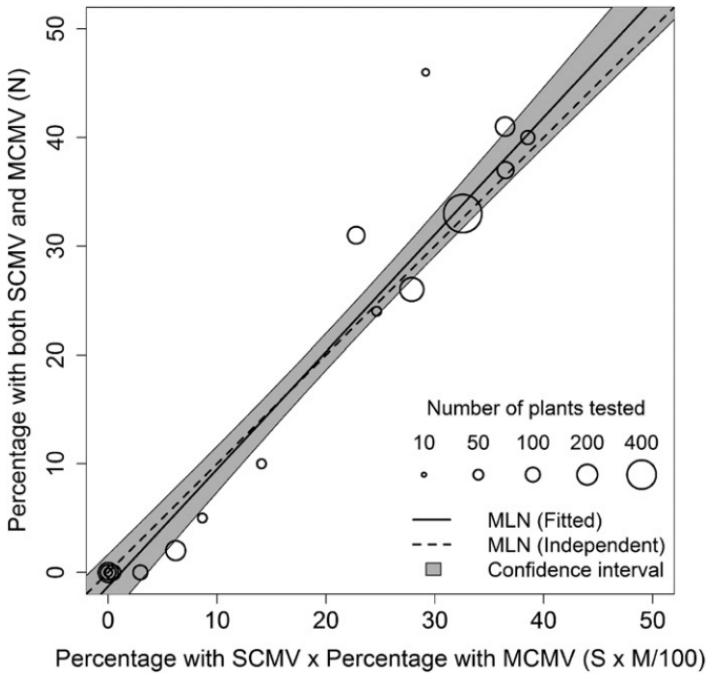


Fig. 3. Field data support the assumption of independent transmission of *Maize chlorotic mottle virus* (MCMV) and *Sugarcane mosaic virus* (SCMV). MLN = maize lethal necrosis. Field data as reported by Mahuku et al. (2015) are replotted, showing the results of survey D in Kenya in 2013 and 2014

$$P(\text{co-infection}) \approx P(\text{infected with SCMV}) \times P(\text{infected with MCMV})$$

INTERACTION TESTS ARE BASED ON INDEPENDENCE

- Methods for cross-sectional data based on **independence** tests
- Simple example:
  - observations ($N = 1000$)

		Pathogen A: Infected	Pathogen A: Not infected	Sum
Pathogen B	Infected	25	175	200
	Not infected	75	725	800
	Sum	100	900	1000

  - Expectation under independence hyp.

		Pathogen A: Infected	Pathogen A: Not infected	Sum
Pathogen B	Infected	20	180	200
	Not infected	80	720	800
	Sum	100	900	1000

  - Chi-square test:

$$\chi^2(1) = 1.74 \Rightarrow p > 0.05 \Rightarrow \text{ no evidence from data the pathogens interact}$$

- May be dressed up in more complex statistics: log-linear or other regressions accounting for confounding factors (e.g. risk group)

QUESTION

Is it right to assume that independence means non-interaction?

SIMPLEST 2 NON-INTERACTING PATHOGENS MODEL

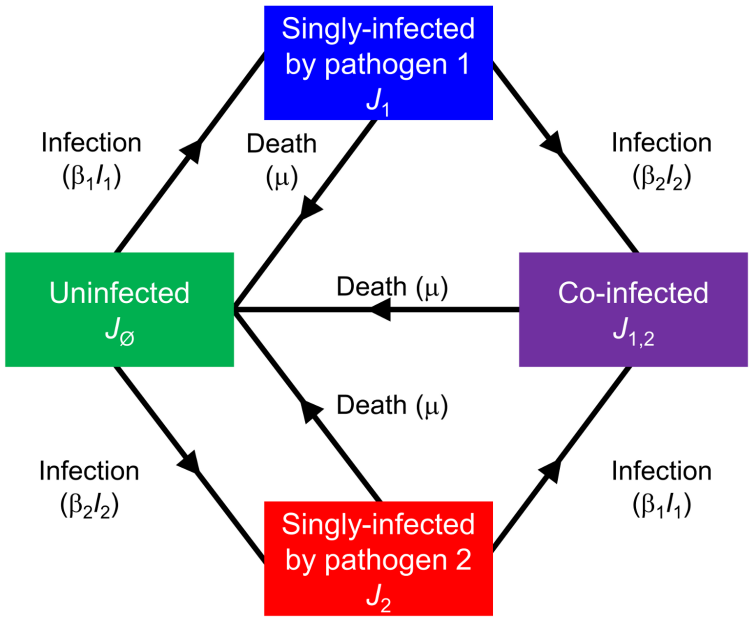
- β_1, β_2: infection rates
- μ: natural death rate
- I_i: prevalence of pathogen $i = 1, 2$

$$\dot{I}_i = \beta_i I_i (1 - I_i) - \mu I_i,$$

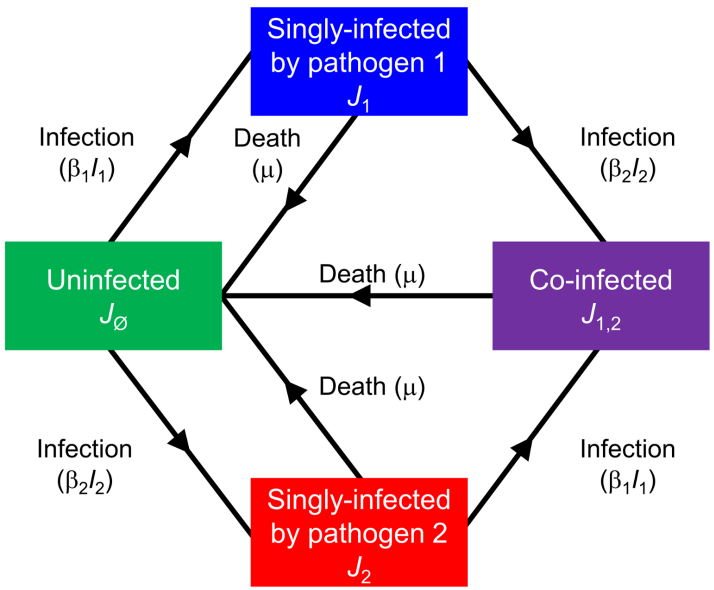
- $F_i = \beta_i I_i = \beta_i (J_i + J_{1,2})$

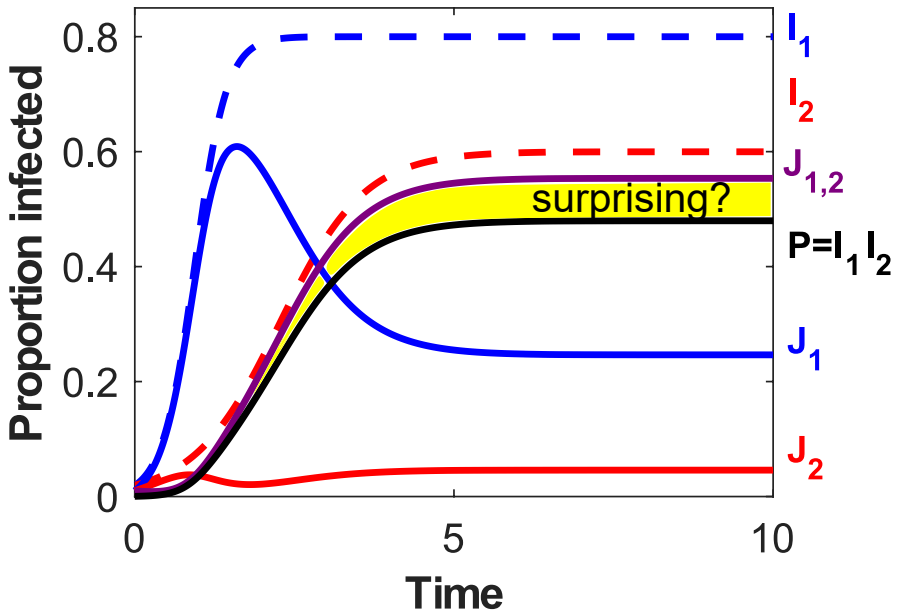
$$\begin{aligned} \dot{J}_1 &= F_1 J_\emptyset - (F_2 + \mu) J_1 \,, \\ \dot{J}_2 &= F_2 J_\emptyset - (F_1 + \mu) J_2 \,, \\ \dot{J}_{1,2} &= F_2 J_1 + F_1 J_2 - \mu J_{1,2} \,. \end{aligned}$$

- $J_\emptyset = 1 - J_1 - J_2 - J_{1,2}$



PREVALENCES ARE NOT MUTIPLICATIVE





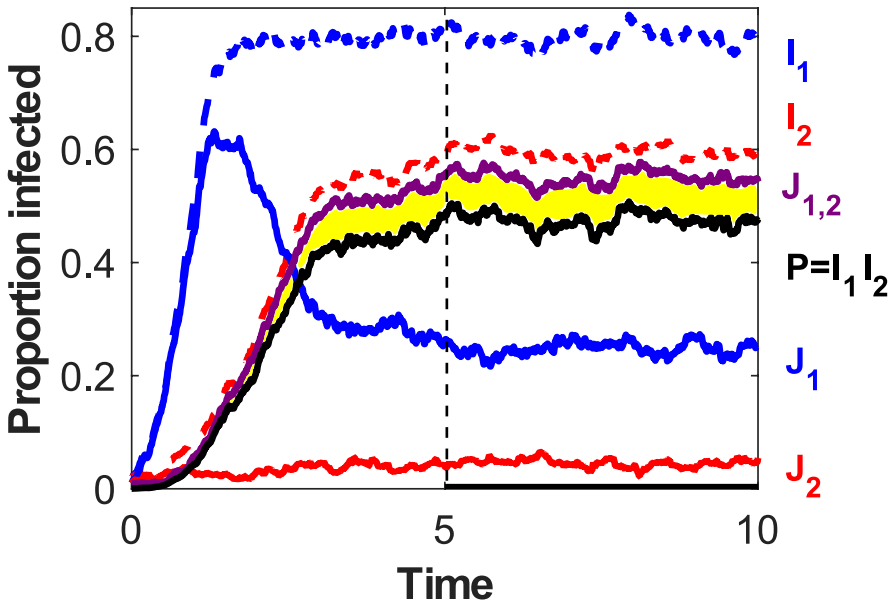
For $R_{0,i} = \beta_i/\mu > 1$, the equilibrium prevalence of co-infection is

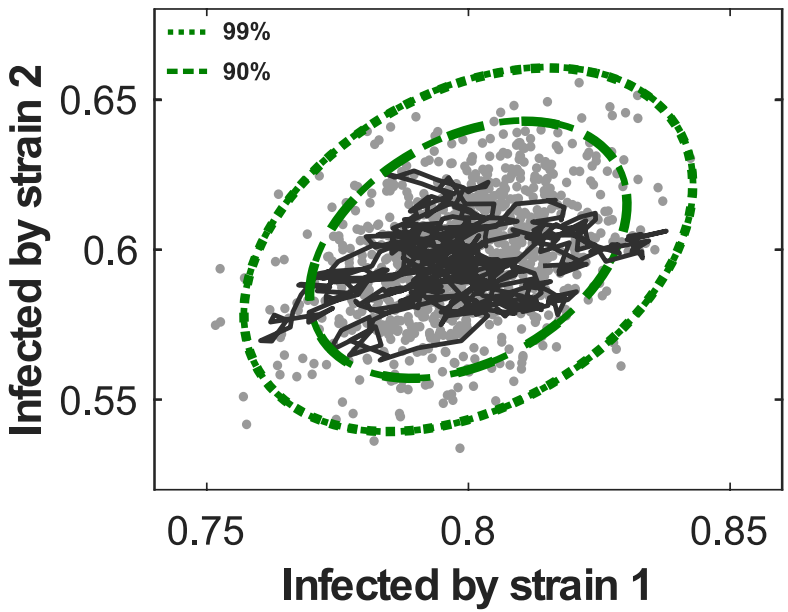
$$\bar{J}_{1,2} = \left(\frac{\beta_1 + \beta_2}{\beta_1 + \beta_2 - \mu} \right) \bar{I}_1 \bar{I}_2 \geq \bar{I}_1 \bar{I}_2 \,.$$

Co-infections are more likely than expected by chance.

PREVALENCES ARE POSITIVELY CORRELATED

Stochastic version: pathogen prevalences correlated





I_1 and I_2 go down simultaneously whenever co-infected dies.

$$\operatorname{cov}\left(\frac{I_1}{N}, \frac{I_2}{N}\right) = \frac{(\beta_1+\beta_2)(\beta_1-\mu)(\beta_2-\mu)\mu}{N\beta_1\beta_2(\beta_1+\beta_2-\mu)(\beta_1-\mu+\beta_2-\mu)} \geq 0\,.$$

APPARENTLY NOT A WELL KNOWN RESULT

May & Nowak (1995)
Proc. Roy. Soc. B
Cited 351 times

Assumes prevalences are multiplicative

Would have been useful to reduce the complexity of co-infection models

Unfortunately this independence assumption is not correct

Box 9.3 SI models accounting for coinfection

With i_j denoting the fraction of individuals harboring strain j (possibly in addition to various other strains), a simple model for coinfection is

$$\frac{di_j}{dt} = i_j[\beta_j(1-i_j) - d - \overline{\alpha}_j], \qquad j = 1, \ldots, n\,. \tag{a}$$

The total population size of hosts is assumed to be held constant, and is normalized to one. The infectivity (transmission rate) of strain j is denoted by β_j. Strain j can invade any host that is not already infected by strain j. Thus $\beta_j i_j(1-i_j)$ is the rate at which new infections with strain j occur.

There is a natural death rate d and a disease induced death rate $\overline{\alpha}_j$ which denotes the average death rates of hosts infected by strain j, and is assumed to be given by the strain with the highest virulence in the host. We define p_j as the probability that a host is not infected with a strain *more* virulent than j. That is,

$$p_j = \prod_{k=j+1}^{n} (1-i_k)\,. \tag{b}$$

Note that $p_n = 1$ and $p_i = (1-i_{j+1})p_{j+1}$. The fraction of hosts that are uninfected is given by $p_0 = \prod_{k=1}^{n}(1-i_k)$. The probability that k is the most virulent strain found in a host is $i_k p_k$, and

$$\overline{\alpha}_j = \alpha_j p_j + \sum_{k=j+1}^{n} \alpha_k i_k p_k\,. \tag{c}$$

This coinfection model is completely defined by Equations (a) to (c). We note that infection and death rules are devised such that if the strains are randomly assorted relative to each other, this continues to be the case, so that Equation (a) remains correct.

Nowak & Sigmund (2002)

KUCHARSKI AND GOG (2012)'S RESULT

- Model reduction in multi-strain influenza models
- Continuous age-structured model
- **Prevalences are multiplicative within infinitesimal age-classes only**: $\forall a > 0$,

$$j_{1,2}(a) = i_1(a) i_2(a)$$

- We recover previous result with $p(a)$ the age distribution:

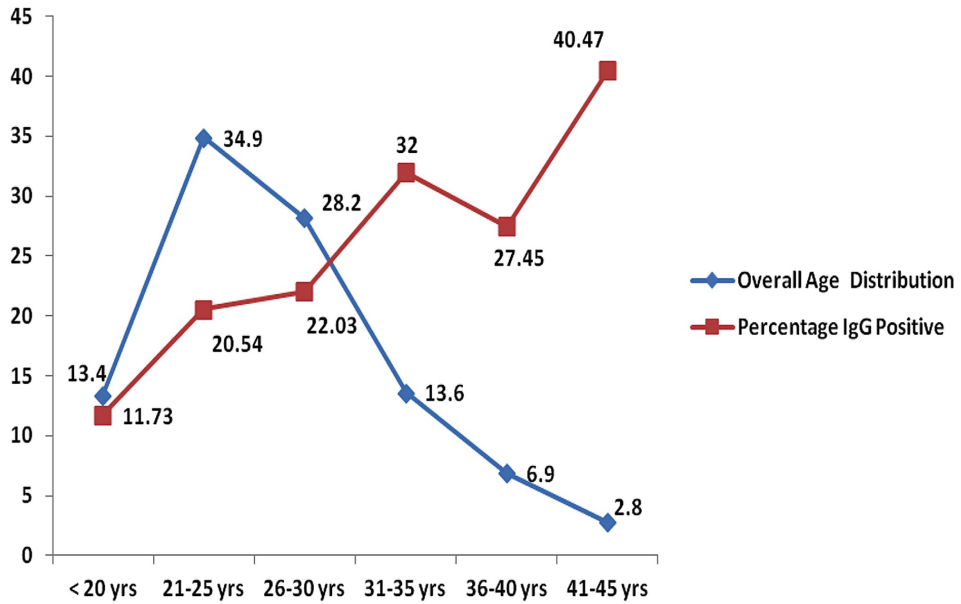
$$\begin{aligned} J_{1,2} &= \int_{\mathbb{R}} j_{1,2}(a) p(a) \mathrm{d}a = \int_{\mathbb{R}} i_1(a) i_2(a) p(a) \mathrm{d}a \\ &\geq \left(\int_{\mathbb{R}} i_1(a) p(a) \mathrm{d}a \right) \left(\int_{\mathbb{R}} i_2(a) p(a) \mathrm{d}a \right) = I_1 I_2 \end{aligned}$$

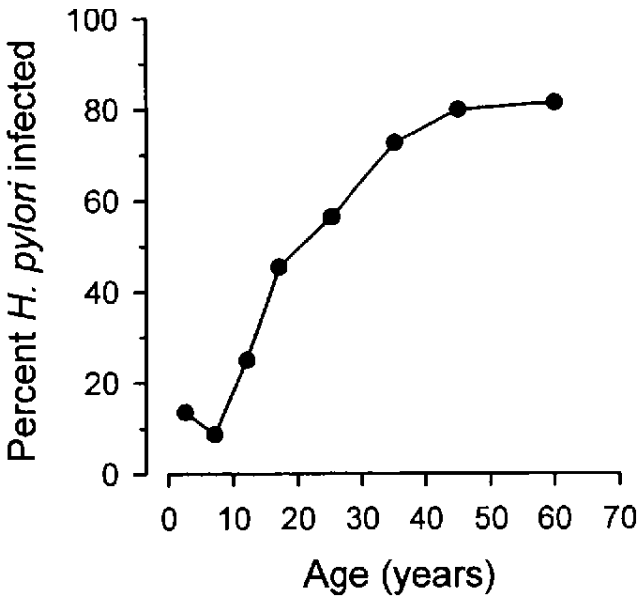
if $i_1(a)$ and $i_2(a)$ are increasing with a (Harris inequality).

KUCHARSKI AND GOG (2012)'S INTERPRETATION

Toxoplasma gondii AND *Helicobacter pylori* AS EXAMPLES

- One way of understanding the result is in terms of aging
- Individuals acquire more infections as they age
- As age increases, so does the probability of being infected
- Therefore, the prevalences of pathogens are correlated





QUESTION

Mathematics say non-interacting pathogens are not independent, but does that change anything in practice?

DATA-DRIVEN TESTS OF PATHOGEN INTERACTIONS

MALARIA AS AN EXAMPLE

Cross-sectional data on co-infection in one of two forms:

1. Full infection profiles

TABLE 2
Distribution of single and mixed infections in the study group*

	Observed (O)			$(E - O)^2$
	n = 590	%	Expected (E)	E
P.f. only	323	54.7	331.6	0.2
P.m. only	1	0.2	20.4	10.0
P.o. only	1	0.2	11.2	10.8
P.f. + P.m.	41	6.9	43.9	0.2
P.f. + P.o.	12	2.0	24.2	6.2
P.m. + P.o.	–	–	1.5	1.5
P.f. + P.m. + P.o.	27	4.6	3.2	177.0
Negative	185	31.4	153.9	6.3

* P.f. = *Plasmodium falciparum*; P.m. = *Plasmodium malariae*; P.o. = *Plasmodium ovale*; – = not detected; $\chi^2 = 219.1$, degrees of freedom = 7, $P < 0.00001$.

$2^3 = 8$ possible combinations of 3 pathogens

2. Multiplicity of infection

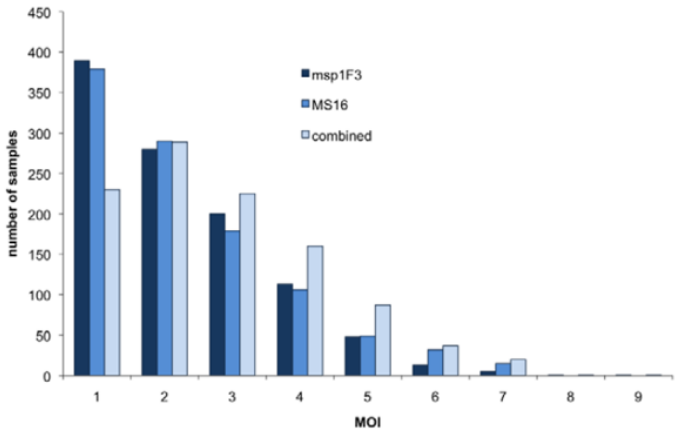


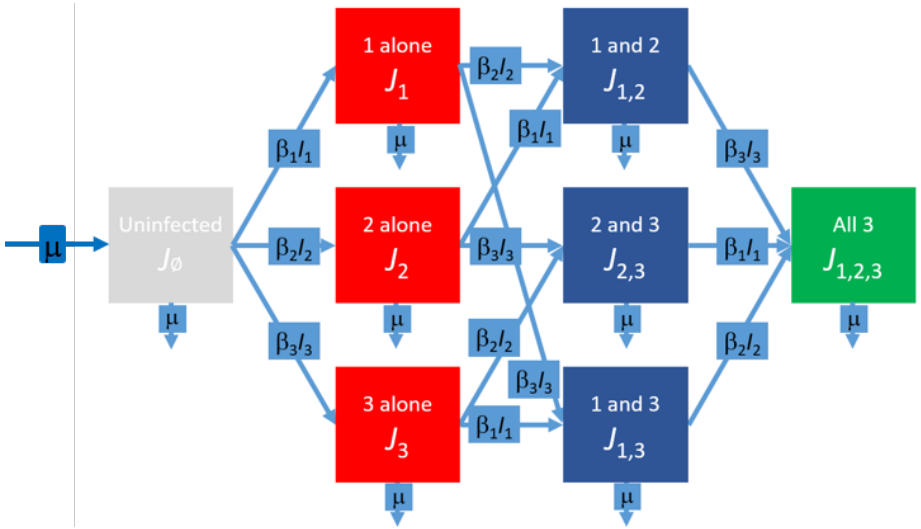
Figure 2. Distribution of multiple clone infections. Distribution of multiplicity of infection as detected by the markers *msp1*F3 and MS16 as well as both markers combined. Only samples with positive results for both markers were included (n = 1050).
doi:10.1371/journal.pntd.0001424.g002

distribution of the number of pathogens hosted per host

1. Non-interacting Distinct Pathogens (NiDP)

- Analogous n pathogen model
- Each pathogen has a distinct

$$R_{0,i} = \frac{\beta_i}{\mu}$$



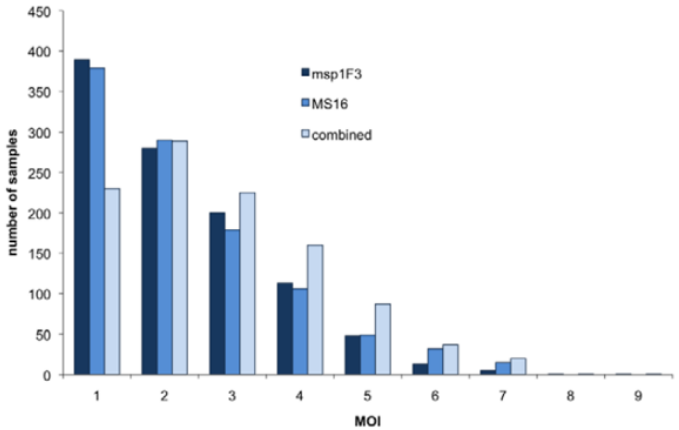
- Find equilibrium values e.g. $I_1 = J_1 + J_{1,2} + J_{1,3} + J_{1,2,3}$
- Simple enough for recursive solution

$$\bar{J}_\Gamma = \frac{\sum_{i\in\Gamma}\left(R_{0,i}-1\right)\bar{J}_{\Omega_i}}{1+\sum_{i\notin\Gamma}\left(R_{0,i}-1\right)}.$$

- Γ: Some combination of pathogens
- $\Omega_i = \Gamma \setminus \{i\}$: One fewer pathogen

2. Non-interacting Similar Pathogens (NiSP)

- **Multiplicity of Infection (MoI) data**: as many parameters in NiDP as data points, so NiDP is overparameterized
- NiSP makes the **strong assumption** that all **pathogens are interchangeable**: $R_{0,i} = R_0$ (1 parameter, more parsimonious).



Probability individual carries k distinct infections given n pathogens in total

Leads to even simpler recursive solution:

$$\bar{M}_k = \frac{(n-k+1)(R_0-1)}{(n-k)(R_0-1)+1}\bar{M}_{k-1}\,.$$

USING THE MODELS IN PRACTICE ON REAL DATA

Form of model – NiDP or NiSP – **driven by data** (and whether or not NiSP assumption of equal R_0 acceptable)

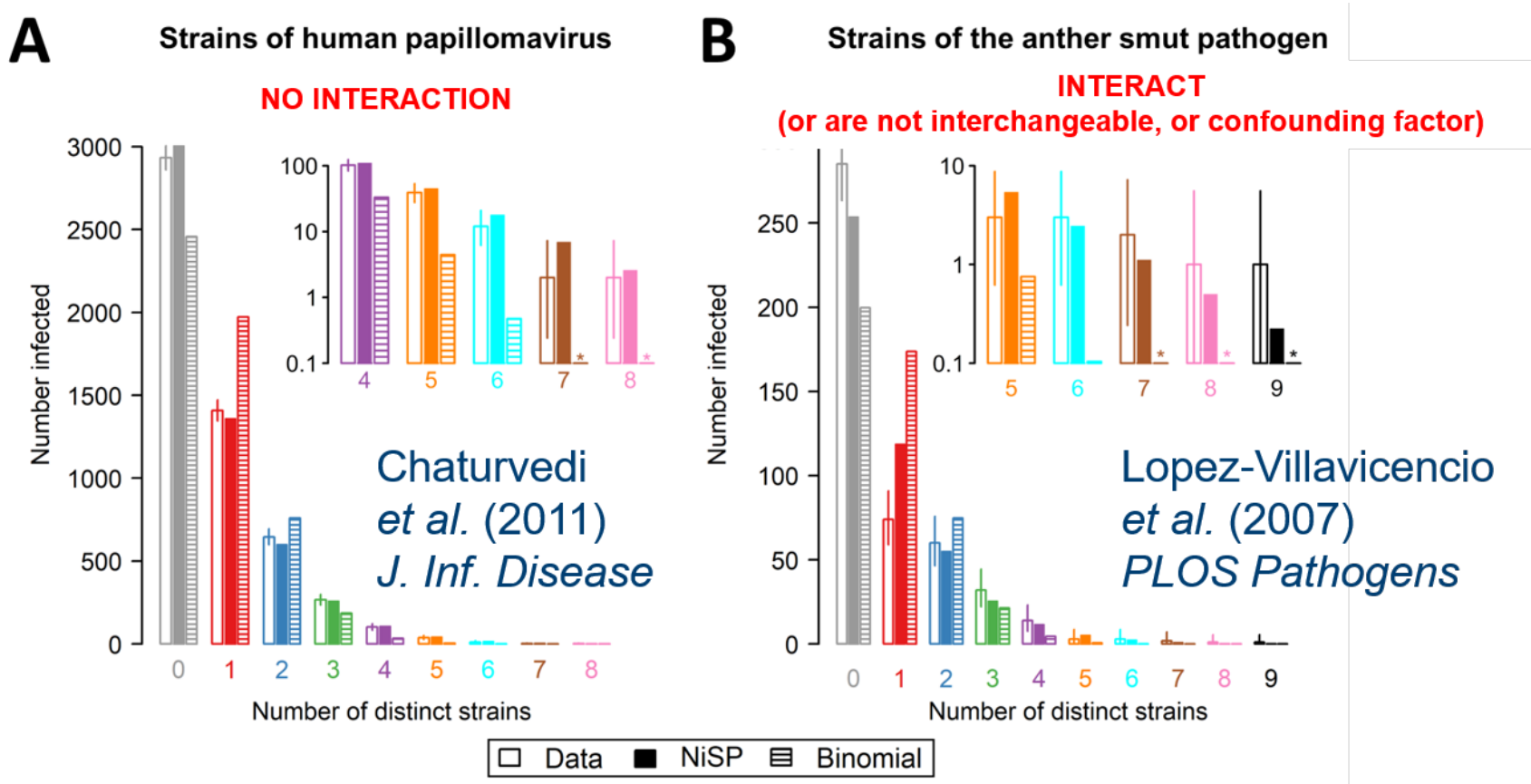
Compare fit of model against bi/multi-nomial distributions

- i.e. **compare against assuming statistical independence**
- fit models via maximum likelihood
- compare using AIC

Test whether NiSP or NiDP is sufficient to explain the data, i.e. test whether data shows evidence of interaction

- Monte Carlo goodness of fit test
- Repeatedly simulate fitted model and check if likelihood of the data is too far in the tail of distribution over all sims

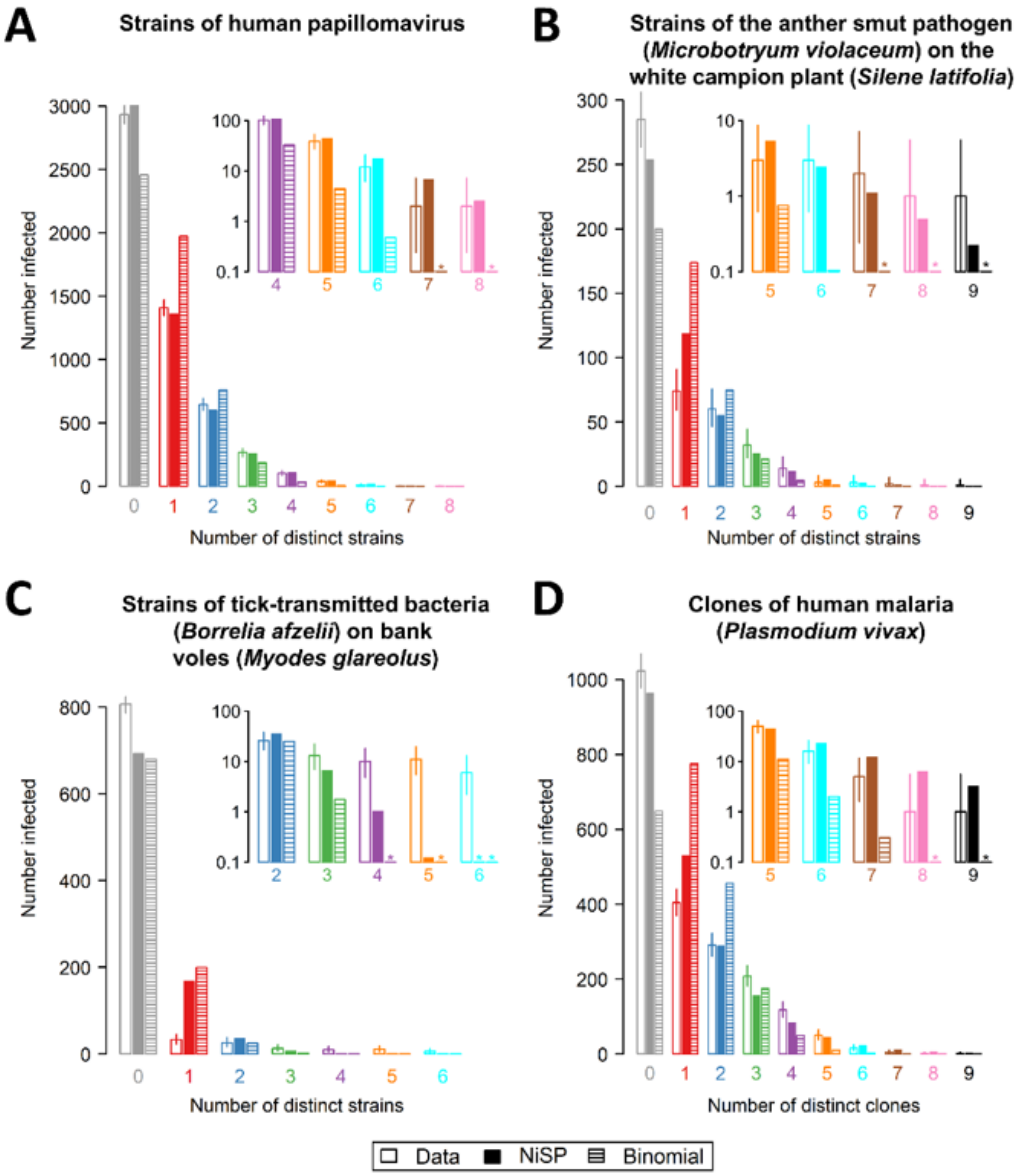
USING THE NiSP MODEL TO UNDERSTAND MOI DATA



ΔAIC = 572.8, p(GoF) = 0.08,
n = 25 (strains), N = 5412 (hosts)

ΔAIC = 158.6, p(GoF) < 0.001,
n = 102 (strains), N = 475 (hosts)

USING THE NiSP CT'D



NiSP outperforms binomial

- in all cases
- particularly in the tails (co-infection much more frequent than expected)

For HPV (Panel A)

- goodness of fit
- i.e. data set consistent with idea types of HPV do not interact

Lack of fit in other cases meaning either:

- interaction
- epidemiological differences between pathogens (recall NiSP assumes equal R0)
- confounding factor (other than age)

USING NIDP TO UNDERSTAND INFECTION PROFILES

MALARIA AS AN EXAMPLE

3 species: *Plasmodium falciparum*, *P. malariae*, *P. ovale*

Am. J. Trop. Med. Hyg., 29(5), 1980, pp. 725–737

A LONGITUDINAL STUDY OF HUMAN MALARIA IN THE WEST AFRICAN SAVANNA IN THE ABSENCE OF CONTROL MEASURES: RELATIONSHIPS BETWEEN DIFFERENT *PLASMODIUM* SPECIES, IN PARTICULAR *P. FALCIPARUM* AND *P. MALARIAE**

LOUIS MOLINEAUX, JOHN STOREY, JOEL E. COHEN,† AND ANTHONY THOMAS
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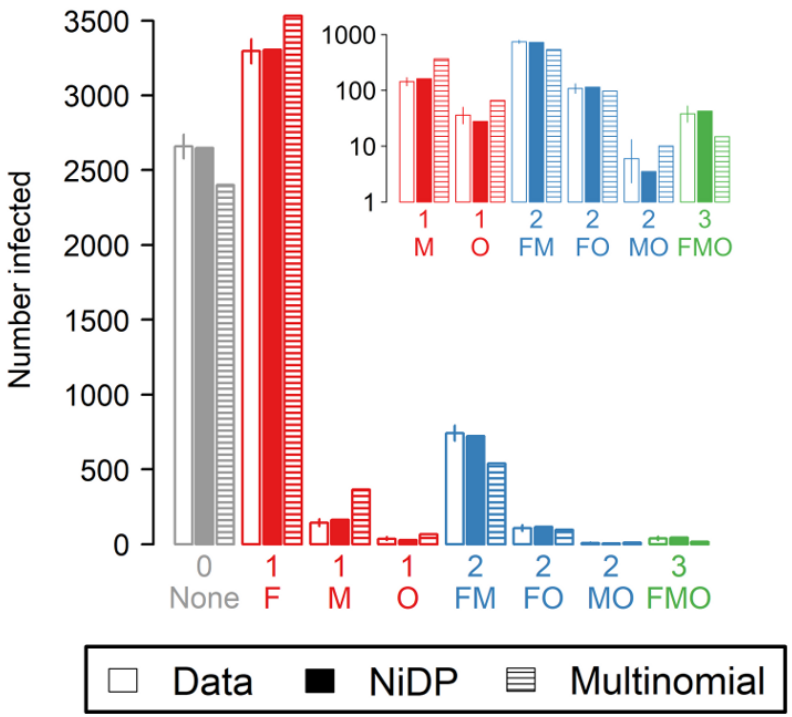
Abstract. The research project on the epidemiology and control of malaria conducted in the Garki District, Kano State, jointly by the Government of Nigeria and the World Health Organization included among its objectives the study of the baseline epidemiology prior to the introduction of any control measures. The present paper analyzes the project's data with respect to the relationships among the three species of *Plasmodium* present, *P. falciparum*, *P. malariae* and *P. ovale*. Parasitemia with *P. falciparum* or *P. malariae* is more likely in the presence than in the absence of the other species. Among persons positive for *P. falciparum*, those with a higher density of parasitemia are more likely to have *P. malariae* also than those with a lower density of *P. falciparum* parasitemia. There is a pronounced seasonal alternation in prevalence between *P. falciparum* and *P. malariae*.

$$R_{0,F} = 2.47,\ R_{0,M} = 1.15,$$
$$R_{0,O} = 1.03,\ \Delta\ \text{AIC} = 362.2,$$
$$p(\text{GoF}) = 0.40$$



No evidence from these data that the pathogens **interact**

Revisiting the analysis of Howard et al (2001)

Methods for estimation of associations between multiple species parasite infections

S. C. HOWARD*, C. A. DONNELLY *and* M.-S. CHAN

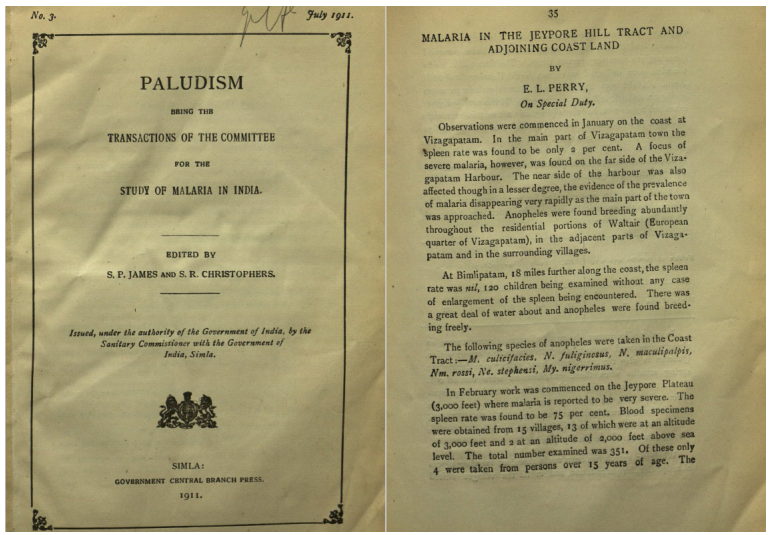
Wellcome Trust Centre for the Epidemiology of Infectious Disease, Department of Zoology, University of Oxford, South Parks Road, Oxford OX1 3FY

No.	Reference	Country	*n*	Ages	Species	Sig. associations
68	Campbell *et al.* (1987)	Kenya	147	Children	FMO	FM$^+$, MO$^+$
69	Campbell *et al.* (1987)	Kenya	142	Children	FMO	FM$^+$, MO$^-$
70	Campbell *et al.* (1987)	Kenya	196	Children	FMO	FM$^+$, MO$^+$
71	May *et al.* (1999)	Nigeria	230	Children	FMO	FM$^+$, MO$^+$
72	May *et al.* (1999)	Nigeria	59	Children	FMO	—
73	May *et al.* (1999)	Nigeria	142	Children	FM	—
74	Leger *et al.* (1923)	Nigeria	250	Children	FMV	FM$^-$
75	Bedier *et al.* (1924)	Nigeria	135	Children	FMV	FM$^-$
76	Knowles & White (1930)	Sierra Leone	809	Children	FMV	FV$^+$, MV$^+$
77	Alifrangis *et al.* (1999)	Tanzania	126	Children	FMO	—
78	Hellgren *et al.* (1994)	Tanzania	163	Children	FMO	—
79	Thomson *et al.* (1994)	The Gambia	1465	Children	FMO	FM$^+$
80	Gbary *et al.* (1988)	Togo	707	Children	FMO	FM$^+$, FO$^+$
81	Brown *et al.* (1970)	Uganda	2899	Children	FM	FM$^+$
82	Dorolle (1927)	China	643	Children	FMV	FV$^-$, MV$^+$
83	Perry (1911)	India	351	Children	FMV	—
84	Phillips (1923)*	India	645	Children	FMV	FV$^-$
85	Aiyer (1924)*	India	57	Children	FMV	—
86	Roy (1926)*	India	309	Children	FV	—
87	Christophers & Shortt (1921)	Iraq	76	Children	FMV	—
88	Lalor (1913)*	Myanmar	207	Children	FMV	FV$^-$
89	Strickland *et al.* (1988)	Pakistan	2891	Children	FV	—
90	Maitland *et al.* (1996)	Vanuatu	292	Children	FV	—
91	Maitland *et al.* (1996)	Vanuatu	211	Children	FV	FV$^-$
92	Maitland *et al.* (1996)	Vanuatu	302	Children	FV	FV$^-$
93	Wilding *et al.* (1995)	Gabon	2192	Mixed	FMO	—
94	Landgraf *et al.* (1994)	Ghana	1048	Mixed	FMO	FM$^-$
95	Deloron *et al.* (1989)	Kenya	222	Mixed	FMO	—
96	Deloron *et al.* (1989)	Kenya	245	Mixed	FMO	—
97	Deloron *et al.* (1989)	Kenya	253	Mixed	FMO	FM$^+$
98	Deloron *et al.* (1989)	Kenya	225	Mixed	FMO	—
99	May *et al.* (1999)	Nigeria	159	Mixed	FMO	—
100	Trape *et al.* (1992)	Senegal	2465	Mixed	FMO	FM$^+$
101	Trape *et al.* (1994)	Senegal	8539	Mixed	FMO	FM$^+$, FO$^+$, MO$^+$
102	Molineaux *et al.* (1980)	Sudan	7026	Mixed	FMO	FM$^+$, FO$^+$, MO$^+$
103	Molineaux *et al.* (1980)	Sudan	6526	Mixed	FMO	FM$^+$, FO$^+$, MO$^+$
104	Nhonoli *et al.* (1974)	Tanzania	360	Mixed	FM	—
105	Nhonoli *et al.* (1974)	Tanzania	450	Mixed	FMV	FM$^+$
106	Wilson (1936)	Tanzania	3393	Mixed	FMV	FM$^+$, FV$^+$, MV$^+$
107	Rosenberg & Maheswary (1982)	Bangladesh	1093	Mixed	FV	FV$^-$

One century of data:

73 data sets on malaria (multiple species), covering a period ranging from 1911 to 1999

Perry, R. (1911). Malaria in the jeypore Hill Tract and adjoining coastland. Paludism, 5, 32.



No. 3. July 1911.

PALUDISM

BEING THE

TRANSACTIONS OF THE COMMITTEE

FOR THE

STUDY OF MALARIA IN INDIA.

EDITED BY

S. P. JAMES AND S. R. CHRISTOPHERS.

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MALARIA IN THE JEYPORE HILL TRACT AND ADJOINING COAST LAND

BY

E. L. PERRY,
On Special Duty.

Observations were commenced in January on the coast at Vizagapatam. In the main part of Vizagapatam town the spleen rate was found to be only 2 per cent. A focus of severe malaria, however, was found on the far side of the Vizagapatam Harbour. The near side of the harbour was also affected though in a lesser degree, the evidence of the prevalence of malaria disappearing very rapidly as the main part of the town was approached. Anopheles were found breeding abundantly throughout the residential portions of Waltair (European quarter of Vizagapatam), in the adjacent parts of Vizagapatam and in the surrounding villages.

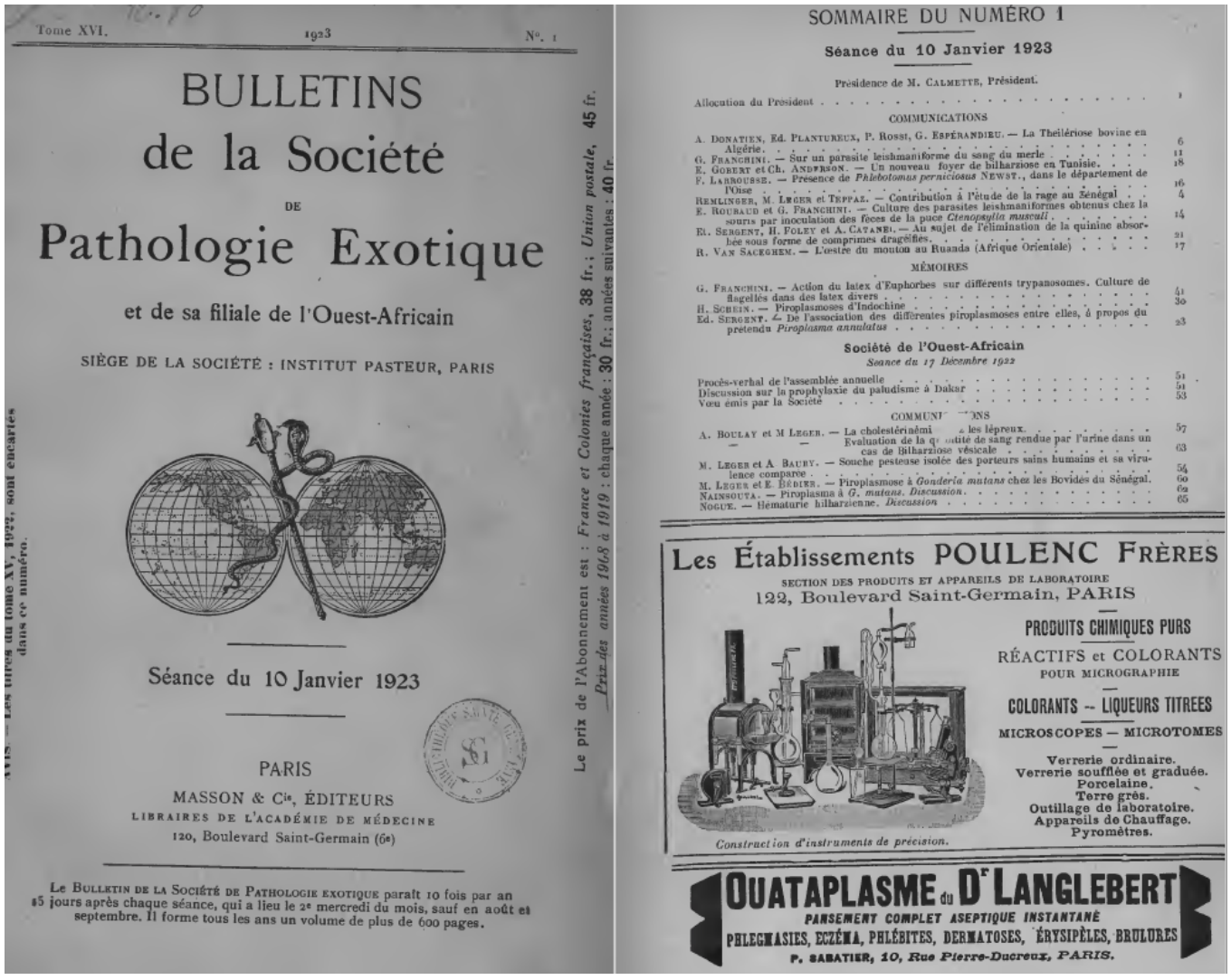
At Bimlipatam, 18 miles further along the coast, the spleen rate was *nil*, 120 children being examined without any case of enlargement of the spleen being encountered. There was a great deal of water about and anopheles were found breeding freely.

The following species of anopheles were taken in the Coast Tract :—*M. culicifacies, N. fuliginosus, N. maculipalpis, Nm. rossi, Ne. stephensi, My. nigerrimus.*

In February work was commenced on the Jeypore Plateau (3,000 feet) where malaria is reported to be very severe. The spleen rate was found to be 75 per cent. Blood specimens were obtained from 15 villages, 13 of which were at an altitude of 3,000 feet and 2 at an altitude of 2,000 feet above sea level. The total number examined was 351. Of these only 4 were taken from persons over 15 years of age. The

Log-linear modelling to find interactions in malaria co-infection data

My role as a French-speaking co-author



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BULLETINS
de la Société
DE
Pathologie Exotique
et de sa filiale de l'Ouest-Africain

SIÈGE DE LA SOCIÉTÉ : INSTITUT PASTEUR, PARIS

Séance du 10 Janvier 1923

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Le Bulletin de la Société de Pathologie exotique paraît 10 fois par an 25 jours après chaque séance, qui a lieu le 2e mercredi du mois, sauf en août et septembre. Il forme tous les ans un volume de plus de 600 pages.

Le prix de l'Abonnement est : *France et Colonies françaises*, 38 fr.; *Union postale*, 45 fr. *Prix des années 1968 à 1919* : chaque année : 30 fr.; années suivantes : 40 fr.

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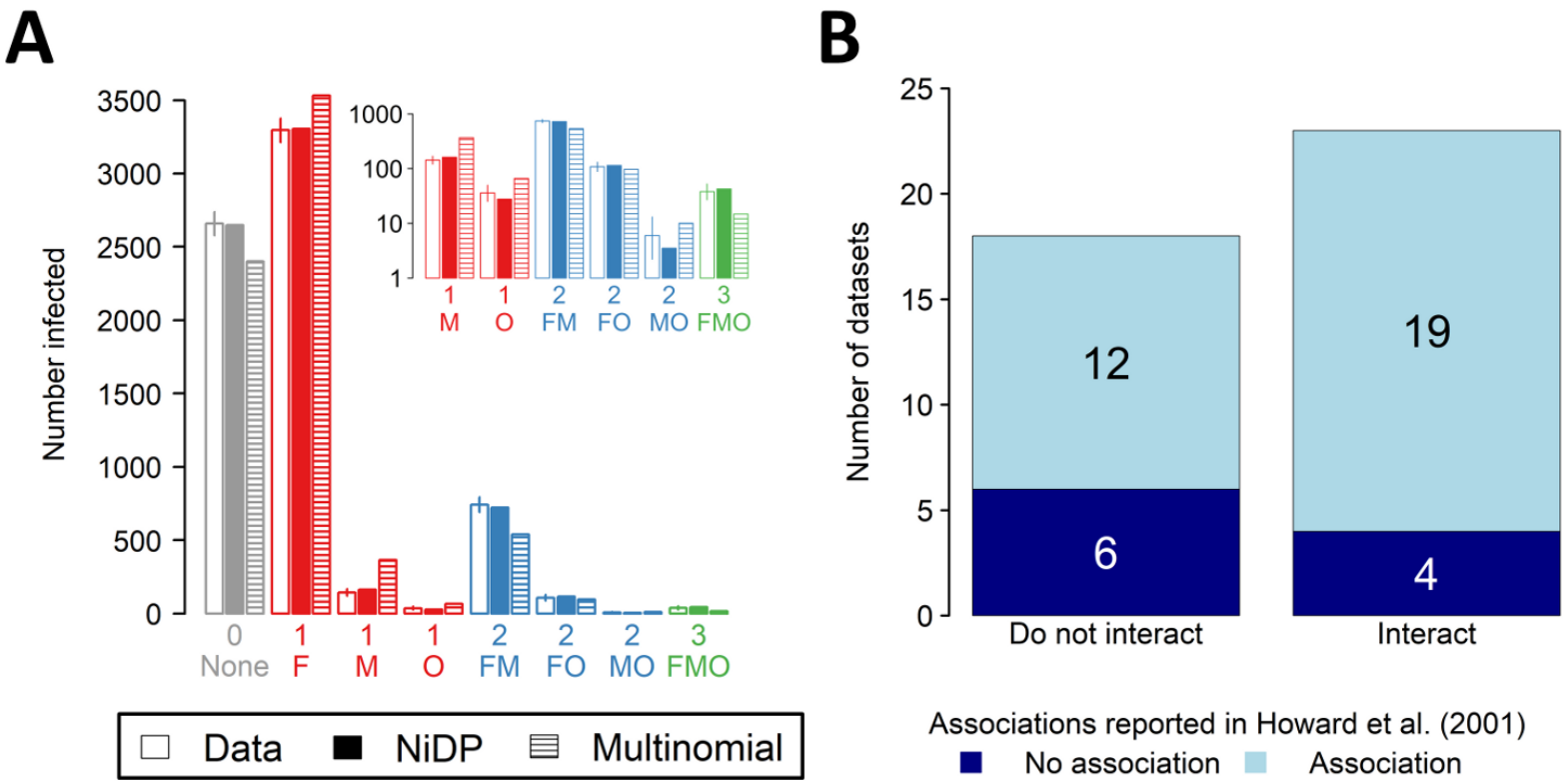
Comparison with Howard et al. (2001)

Results using NiDP **differ** in $(12 + 4)/41 \approx 39\%$ of cases



Testing for interaction differs from independence tests

SUMMARY

Non-interacting pathogen are not statistically independent

- the prevalence of co-infection is always greater than the product of the prevalences (positive correlation)
- statistically independent pathogens may well be interacting (not presented)
- confirms that statistical independence is far from equivalent to the absence of biological interaction between pathogens

Novel interaction tests based on simple epidemic models

- simple models challenge previous methods based on statistical independence
- simple models (with no explicit age structure) intrinsically correct for age as a confounding factor
- epidemic models make it unnecessary to keep track of age

LIMITS AND PROSPECTS

Very simple two parameter SIS model (transmission, mortality)

- the positive correlation is due to host mortality (or ageing)
- **results are valid for chronic (long-lasting) infections**
- which represent a large fraction of co-infections

Clearance

- the model **can accomodate specific pathogen clearance**
- doubles the number of parameters, but may still be fitted
- qualitative results are unchanged in all cases tested

Virulence

- disease-induced mortality was assumed to be zero
- otherwise pathogens interact at the host population scale
- but **virulence could be included in the model** as well

Ecological perspectives

Macro-parasites (e.g. worms)

- Macroparasite data show positive associations between parasites known to interact negatively (Fenton et al 2014)
- SIS models are inedaquate for macro-parasites
- **Our approach could be extended to macroparasites**

Meta-communities

- Pathogens are species which form meta-populations occupying discrete patches (hosts)
- In meta-community ecology, interactions between species are often inferred from co-occurrence data
- Most methods are based on statistical associations
- **Our approach could be extended to metacommunities**

TAKE-HOME MESSAGE

To detect interactions, methods based on

statistical independence
and
random distributions

should be replaced with methods based on

model-based distributions
assuming
no biological interactions

as a null expectation.

THANKS FOR LISTENING!

- The NIMBioS Working Group, particularly
  - Nik Cunniffe (Cambridge)
  - Linda Allen (Texas Tech)
- Hamelin, F. M., Allen, L. J., Bokil, V. A., Gross, L. J., Hilker, F. M., Jeger, M. J., ... & Cunniffe, N. J. (2019). Coinfections by noninteracting pathogens are not independent and require new tests of interaction. PLoS Biology, 17(12).