Workshop: "Statistical modeling of epidemic outbreaks“
AUEB 05.05.2023

Modelling transmission and control of infectious diseases: From HIV and antibiotic resistant bacteria to SARS-CoV-2

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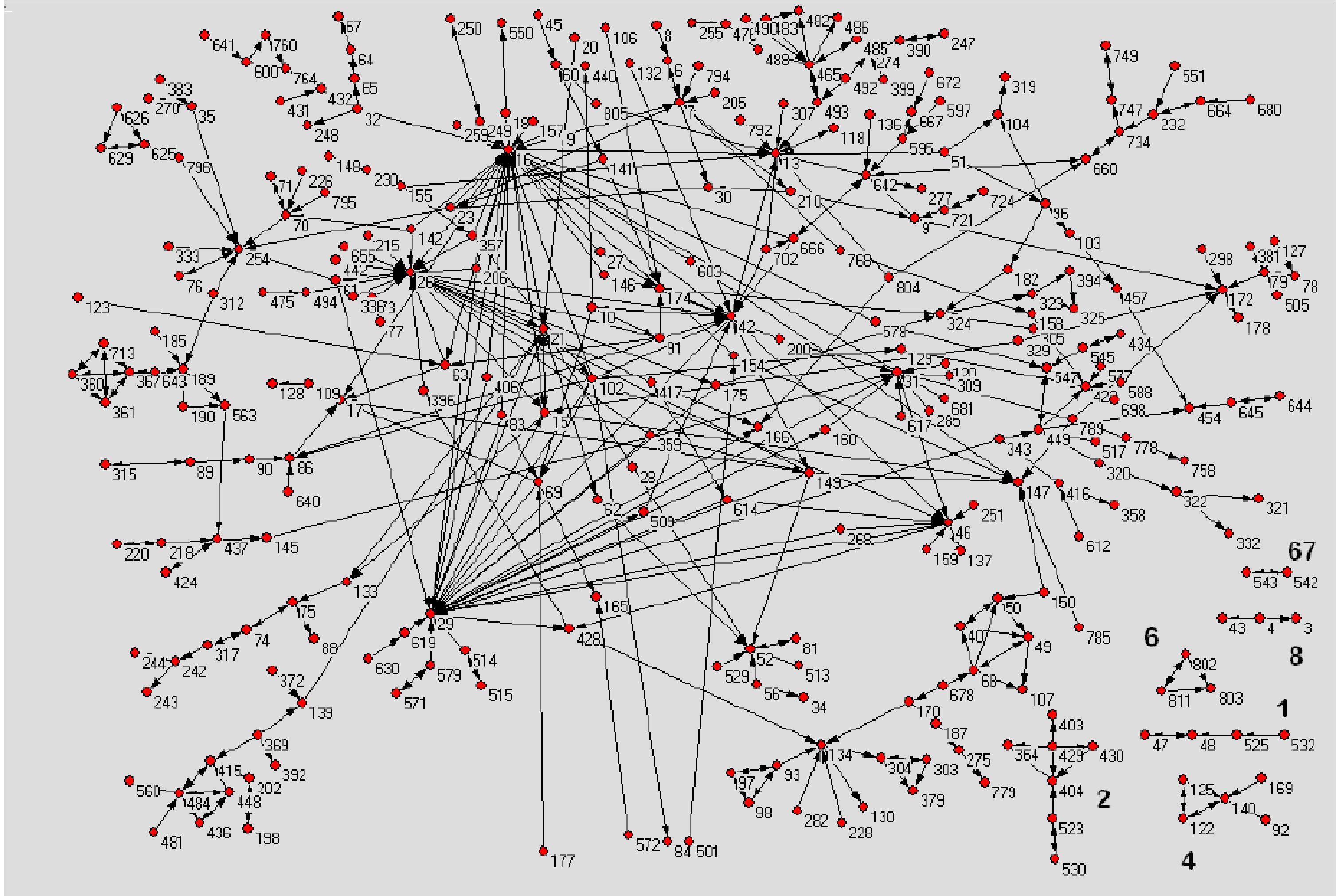
HIV transmission among people who inject drugs

Transmission through injection networks

(though sharing of injection equipment)

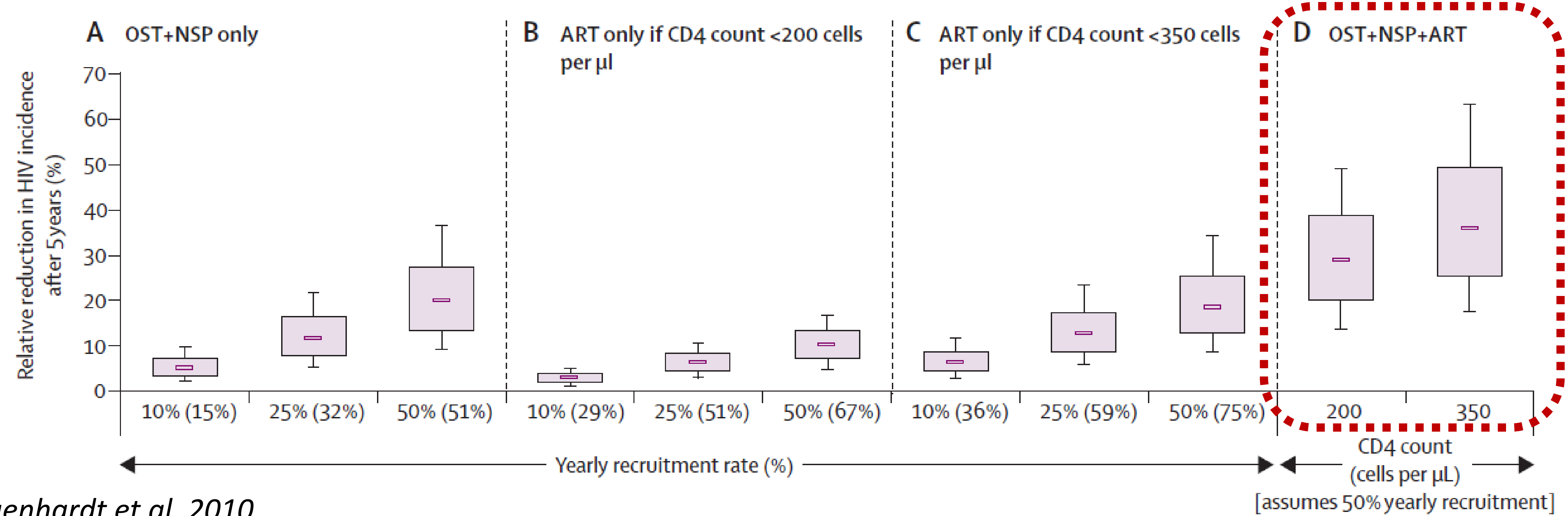
A network of injecting drug use in Brooklyn



(Dombrowski et al, 2007)

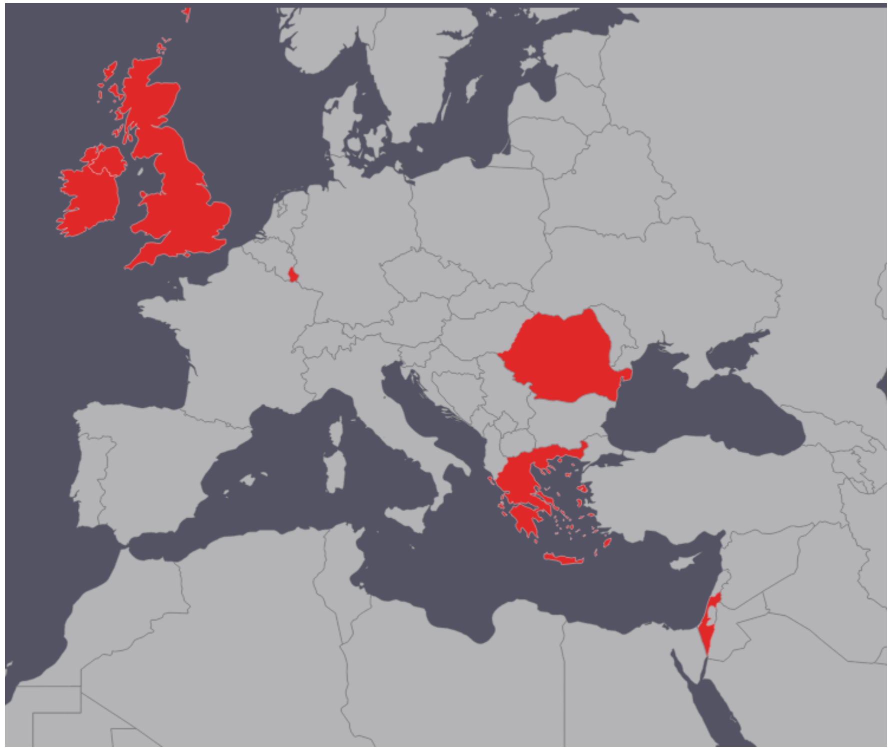
Multiple outbreaks of HIV infection since the 1980s

- To control transmission → **high-coverage combined interventions (harm reduction)**
  - Distribution of clean syringes (needle and syringe programs)
  - Opioid agonist treatment (methadone, buprenorphine)
  - Linkage to antiretroviral treatment for HIV (Undetectable=Untransmissible)



Degenhardt et al, 2010

A new generation of HIV outbreaks among PWID: 2011 - today

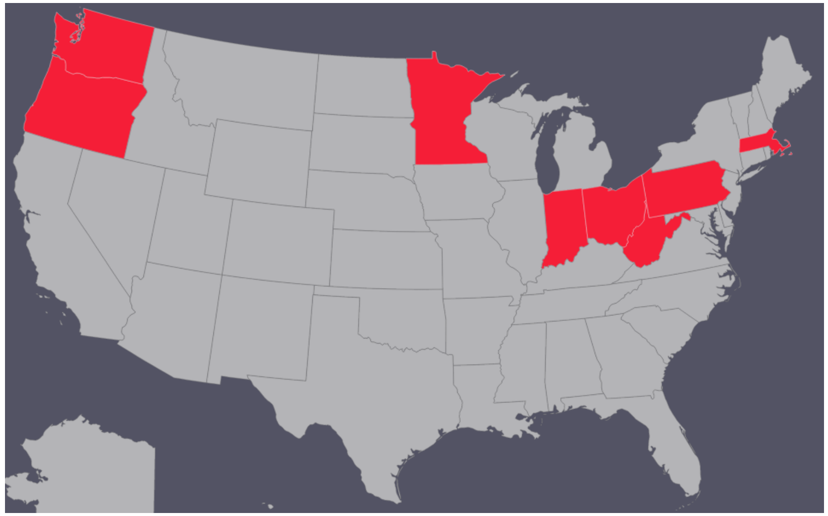


Europe & Middle East

Athens, Greece (**2011**)
Bucharest, Romania (2011)
Tel Aviv, Israel (2012)
Luxembourg (2013)
Dublin, Ireland (2014)
Glasgow, Scotland, UK (2015)
Thessaloniki, Greece (**2020**)

North America

Indiana (2014)
Massachusetts (2015)
Saskatchewan, Canada (2016), Ohio (2017)
Minnesota, West Virginia, Oregon, Washington, Pennsylvania (2018)



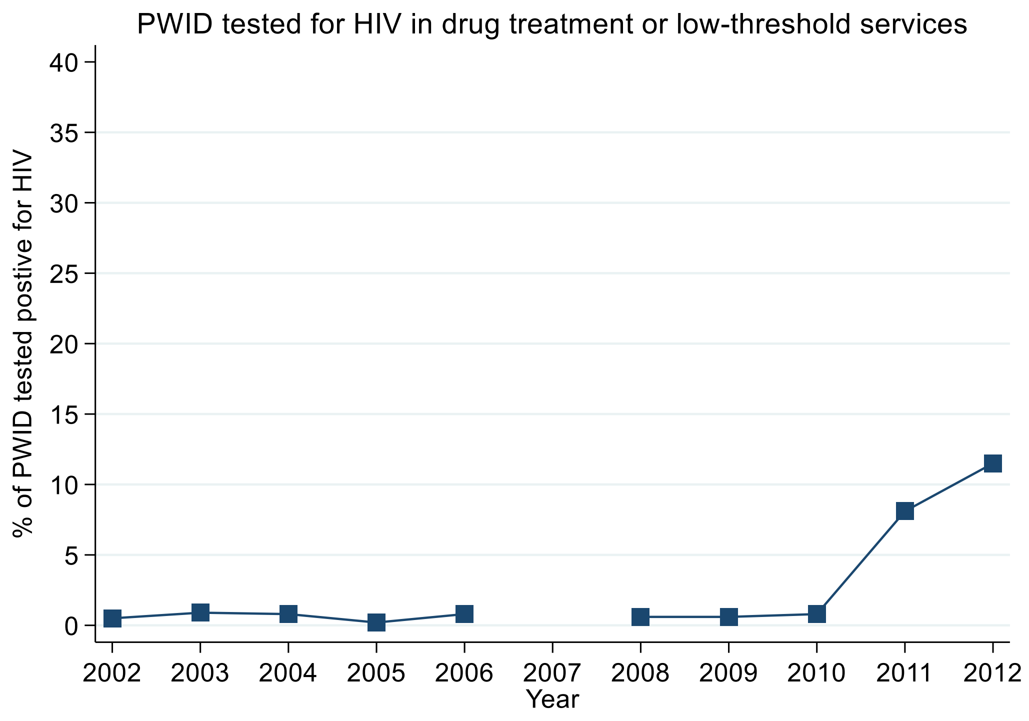
Athens outbreak, 2011-2013

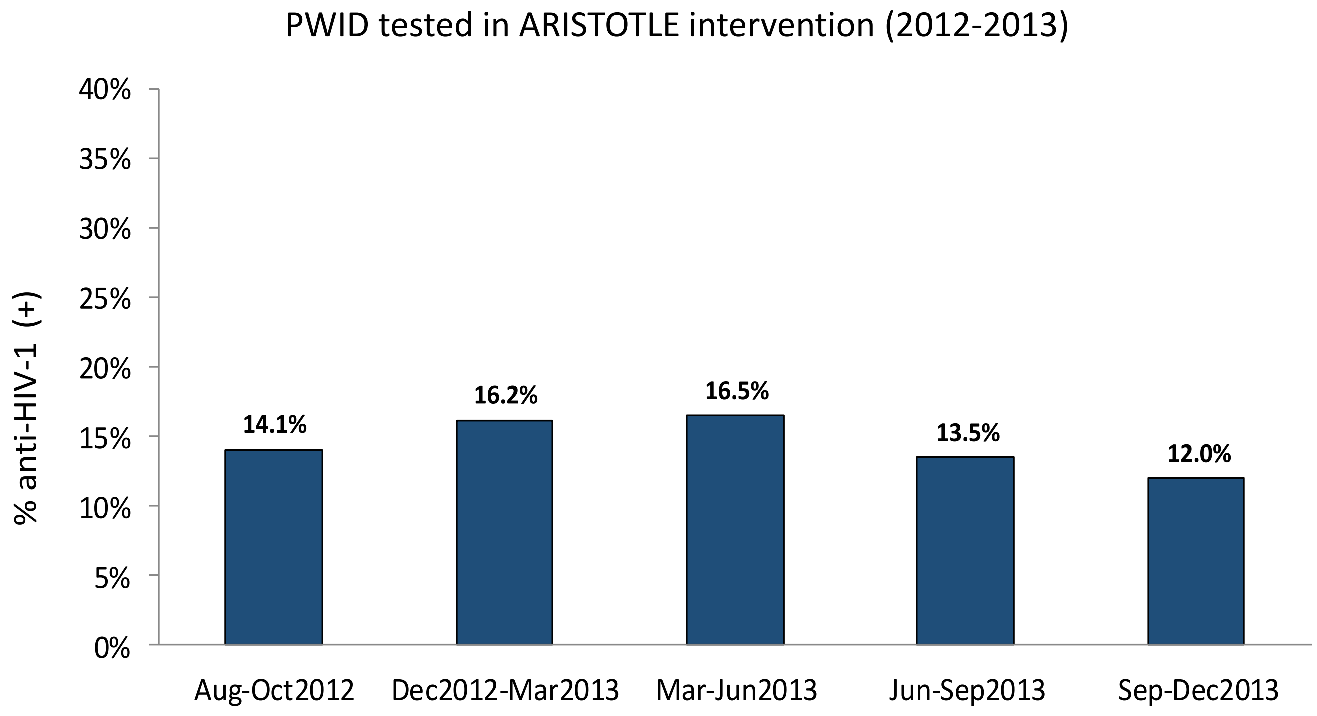
- The largest HIV outbreak in this population in Western Europe and North America since 2010
- Multiple interventions were implemented in response to the outbreak
  - Increase in coverage of syringe distribution & opioid agonist treatment
  - A seek-test-treat intervention (**ARISTOTLE** program) aiming at reaching this hard-to-reach population & to diagnose/link patients to HIV care

Important questions:
How can we reconstruct the course of the outbreak?
How can we assess the impact of these interventions?

What do we know about this outbreak?

Increase in HIV prevalence after 2009

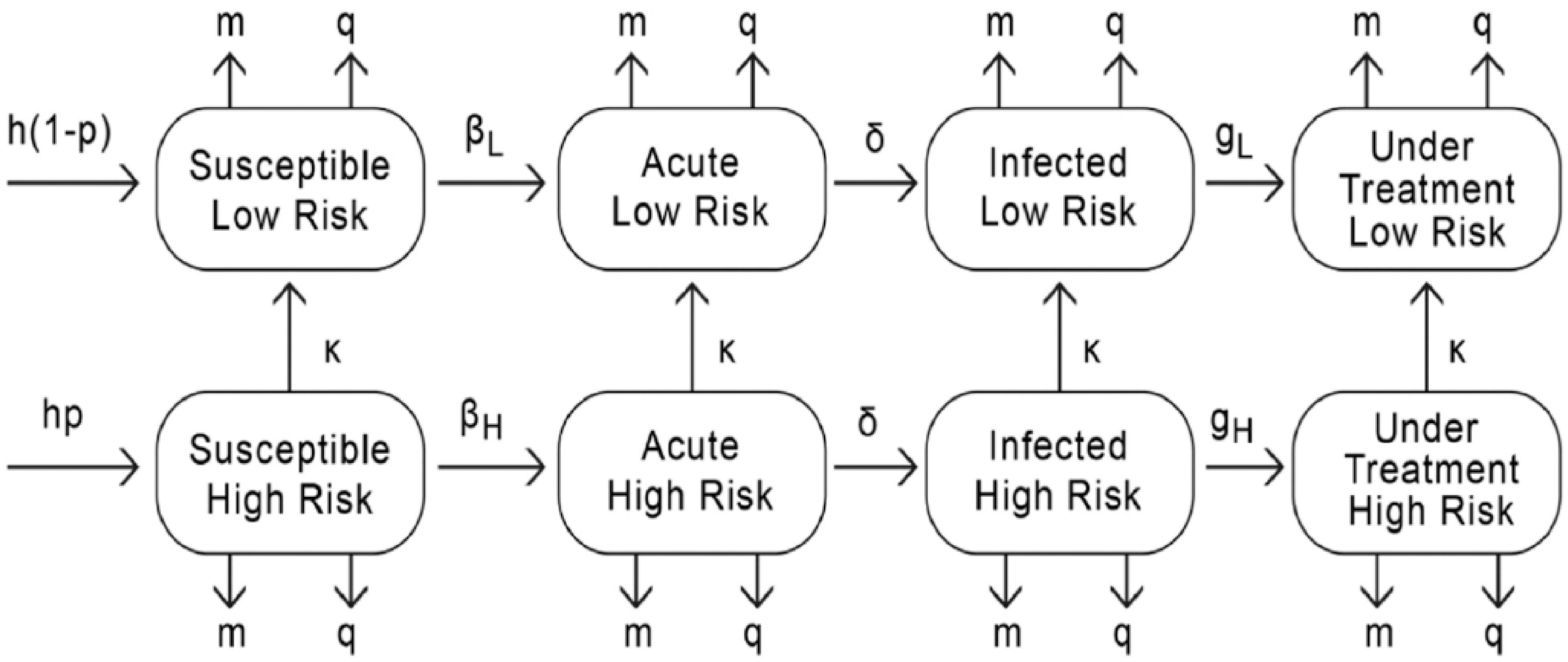




Paraskevis et al, 2011

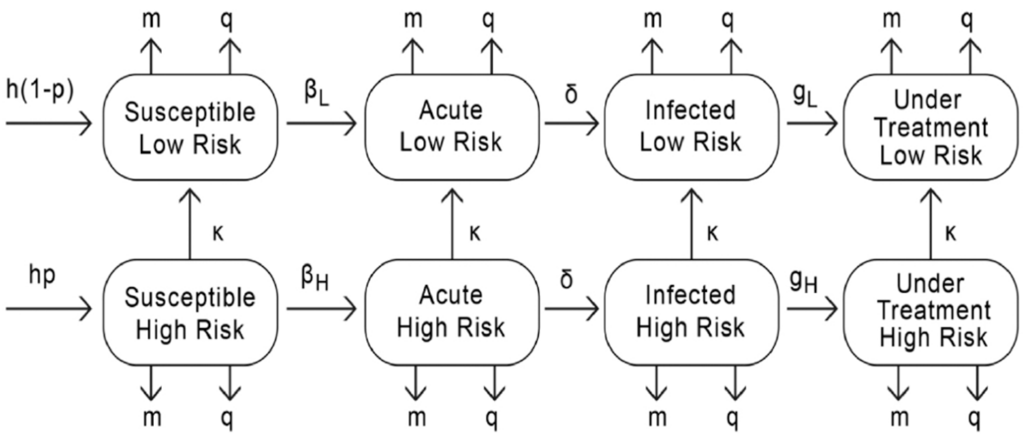
Sypsa et al, 2017

Modelling the outbreak & the impact of interventions



Flountzi et al, 2022

Modelling the outbreak & the impact of interventions



- Some parameters from the literature or from data collected during ARISTOTLE program
- Other parameters estimated by fitting the model to data on:
  1. HIV prevalence
  2. Proportion of HIV infected on antiretroviral treatment
  3. Proportion transitioning from high risk to low risk

Flountzi et al, 2022

System of differential equations for the model

PWID Low Risk:

$$\frac{dS_L}{dt} = h(1-p)N - \Omega(t)S_L\beta_L(rH_L + I_L + wA_L)/N - (m+q)S_L + \kappa S_H$$

$$\frac{dH_L}{dt} = \Omega(t)S_L\beta_L(rH_L + I_L + wA_L)/N - (m+q+\delta)H_L + \kappa H_H$$

$$\frac{dI_L}{dt} = -(m+q+g_L)I_L + \kappa I_H + \delta H_L$$

$$\frac{dA_L}{dt} = g_L I_L - (m+q)A_L + \kappa A_H$$

PWID High Risk:

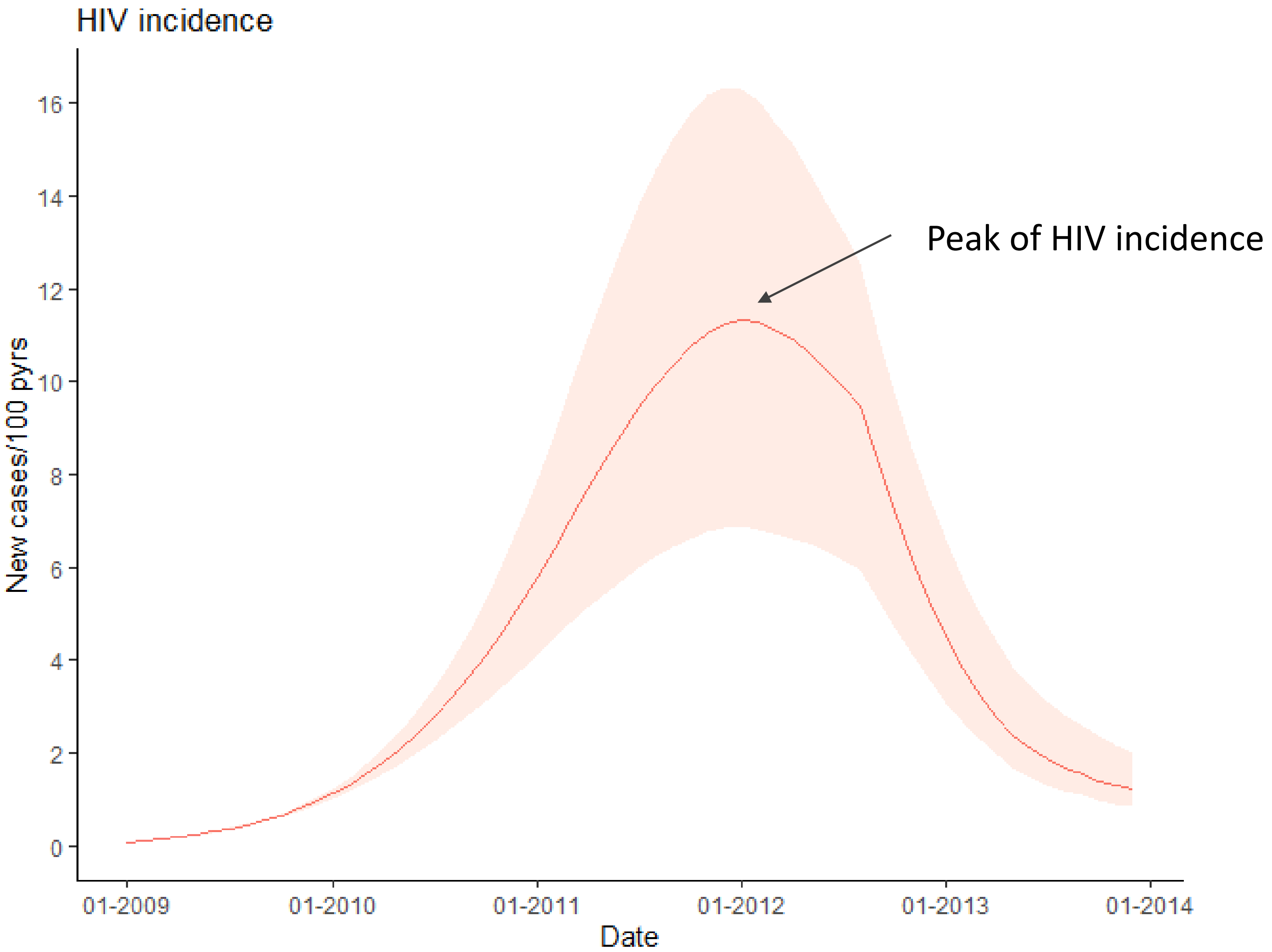
$$\frac{dS_H}{dt} = hpN - \Omega(t)S_H\beta_H(rH_H + I_H + wA_H)/N - (m+q+\kappa)S_H$$

$$\frac{dH_H}{dt} = \Omega(t)S_H\beta_H(rH_H + I_H + wA_H)/N - (m+q+\delta+\kappa)H_H$$

$$\frac{dI_H}{dt} = -(m+q+g_H+\kappa)I_H + \delta H_H$$

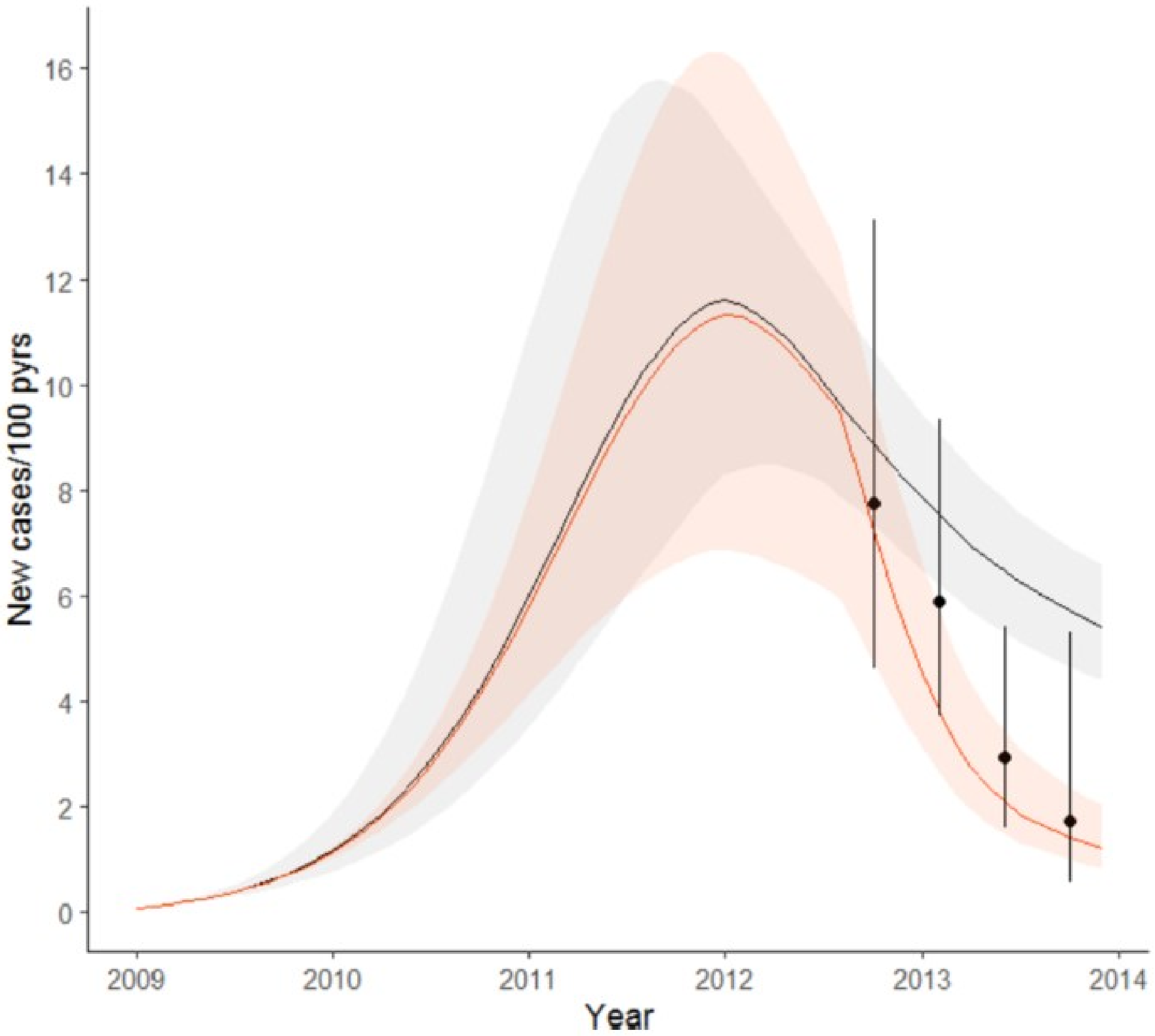
$$\frac{dA_H}{dt} = g_H I_H - (m+q+\kappa)A_H$$

Reconstructing the course of the HIV outbreak



Flountzi et al, 2022

Assessing the impact of interventions on HIV incidence



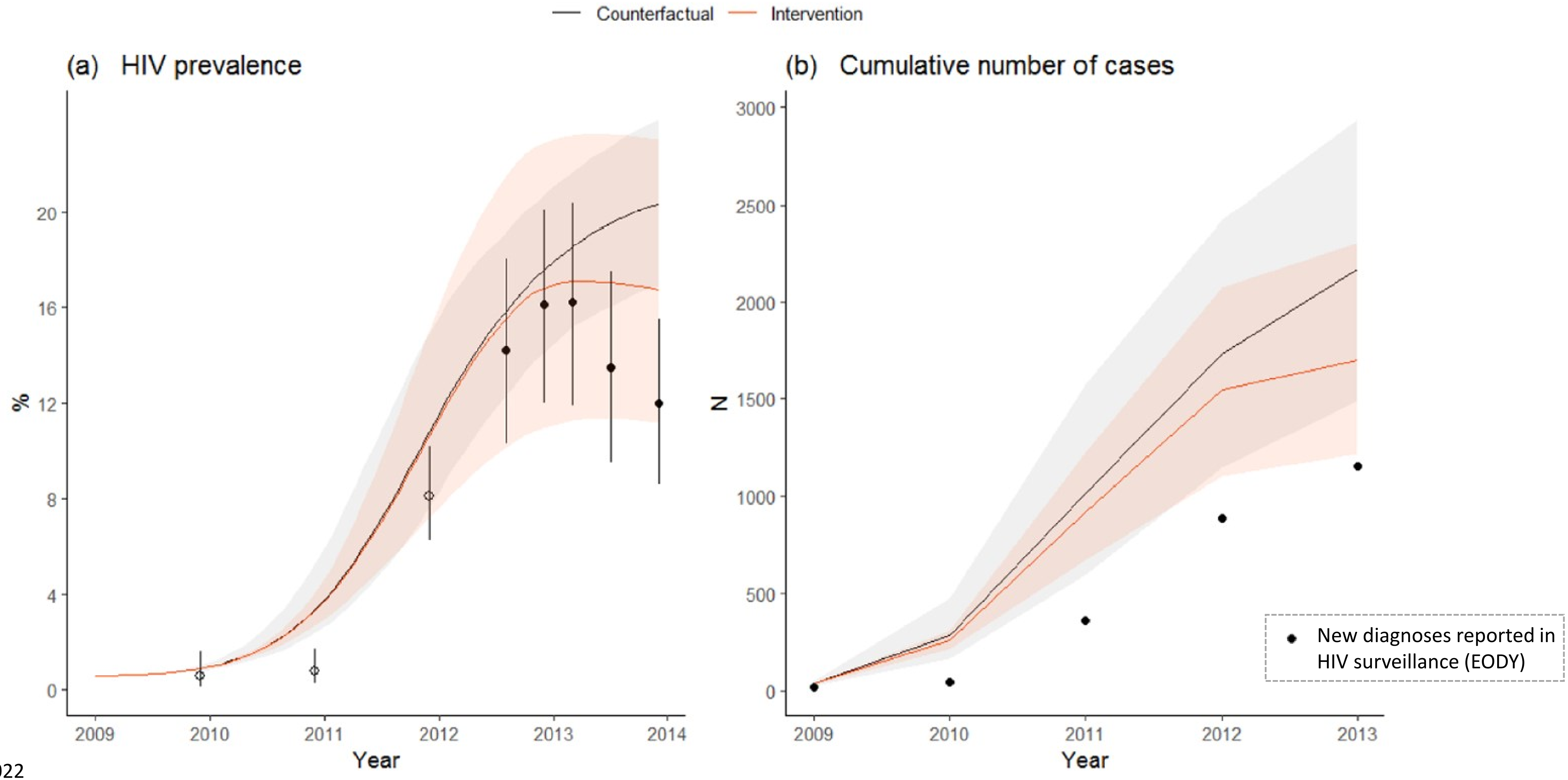
Counterfactual scenario: Only limited scale-up of syringe distribution

77% lower

ARISTOTLE &
scale-up of harm reduction

Flountzi et al, 2022

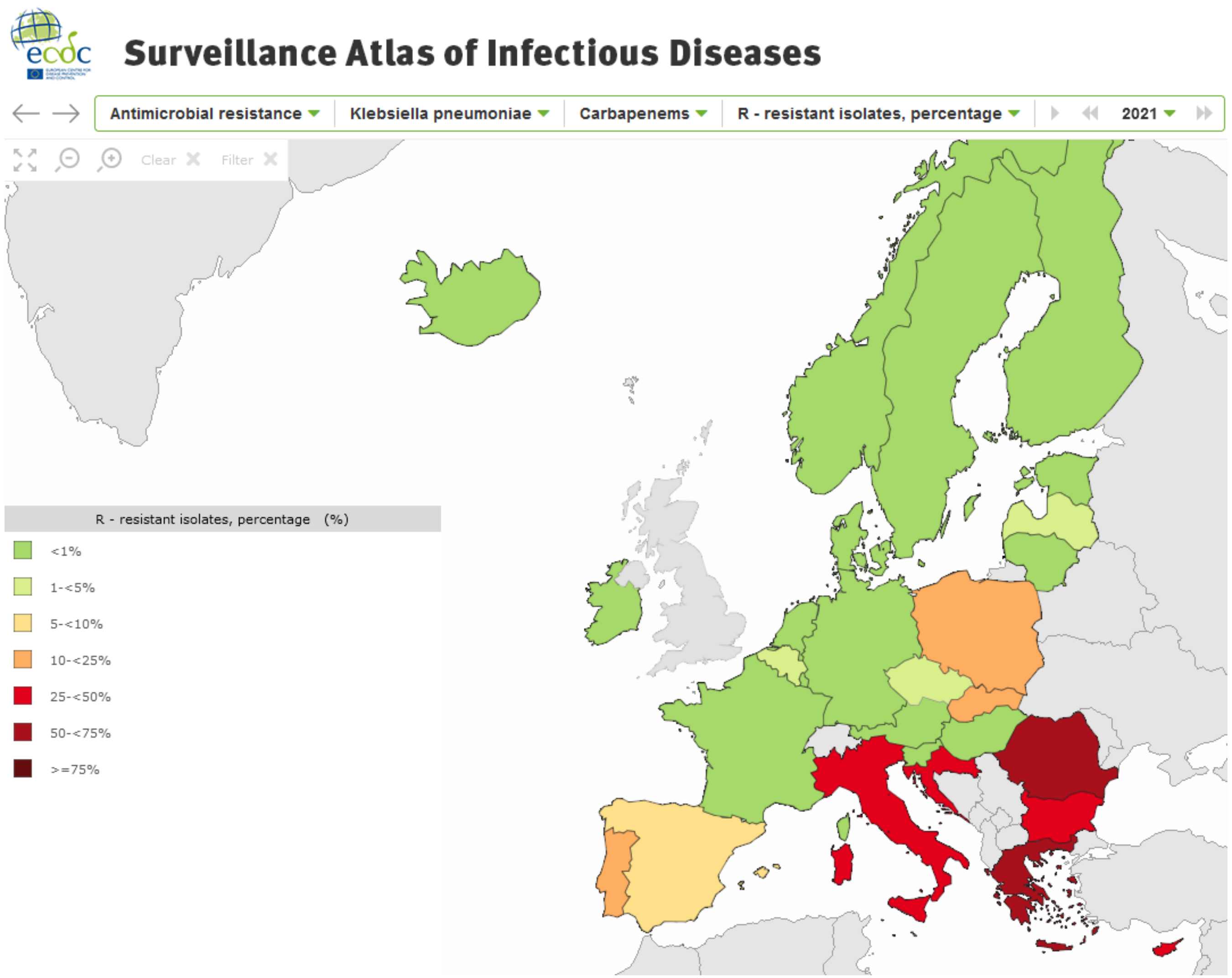
Assessing the impact of interventions on HIV prevalence and on the cumulative number of cases



Flountzi et al, 2022

Transmission of antibiotic resistant bacteria in the healthcare setting:

The example of Carbapenemase-Producing Klebsiella Pneumoniae (CPKP) in a Greek hospital



Case Reports > Diagn Microbiol Infect Dis. 2013 Mar;75(3):317-9.
doi: 10.1016/j.diagmicrobio.2012.12.003. Epub 2013 Jan 11.

The characteristics of Klebsiella pneumoniae that produce KPC-2 imported from Greece

Wilson W Chan [1], Gisele Peirano, Daniel J Smyth, Johann D D Pitout

Affiliations + expand

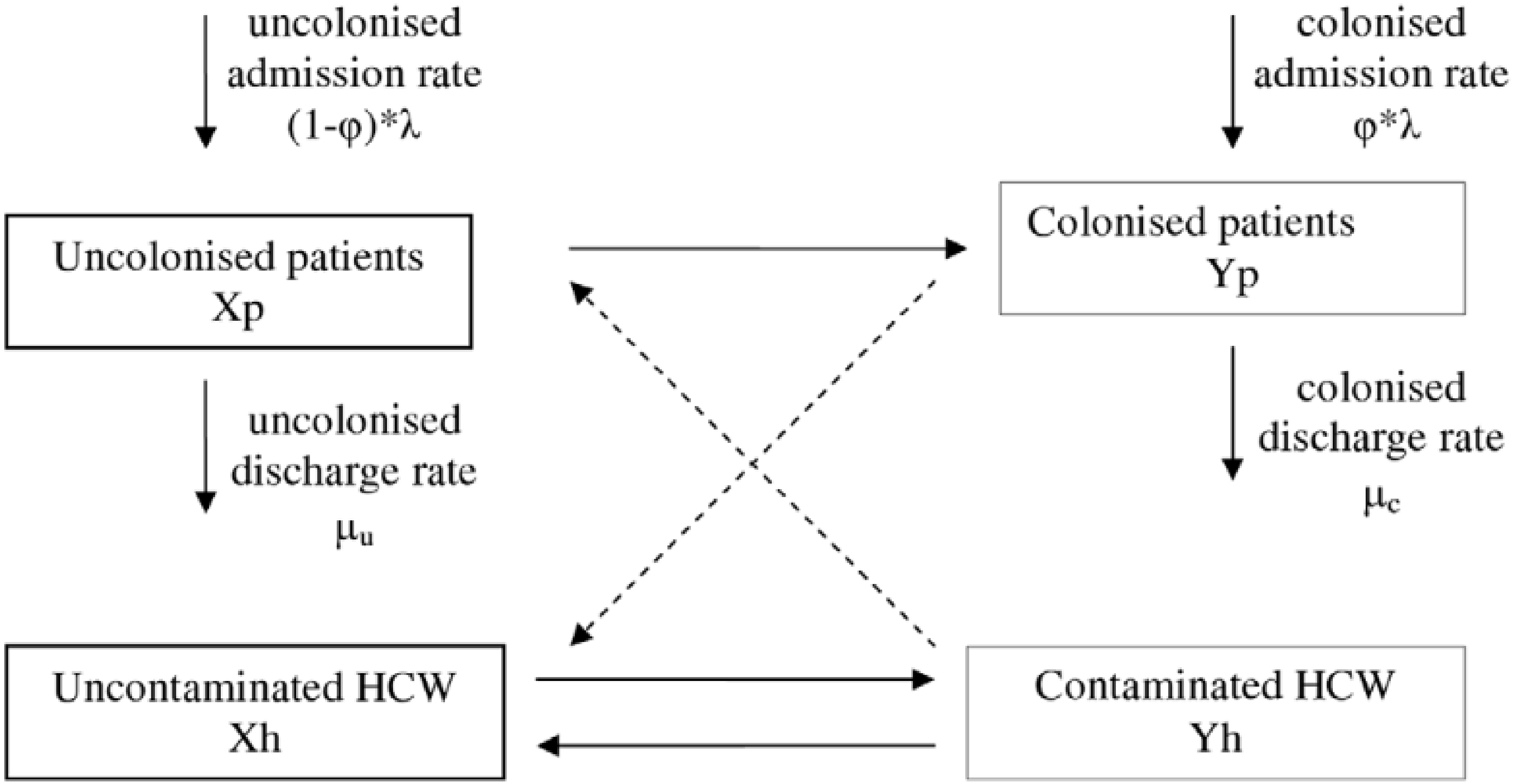
PMID: 23313083 DOI: 10.1016/j.diagmicrobio.2012.12.003

Abstract

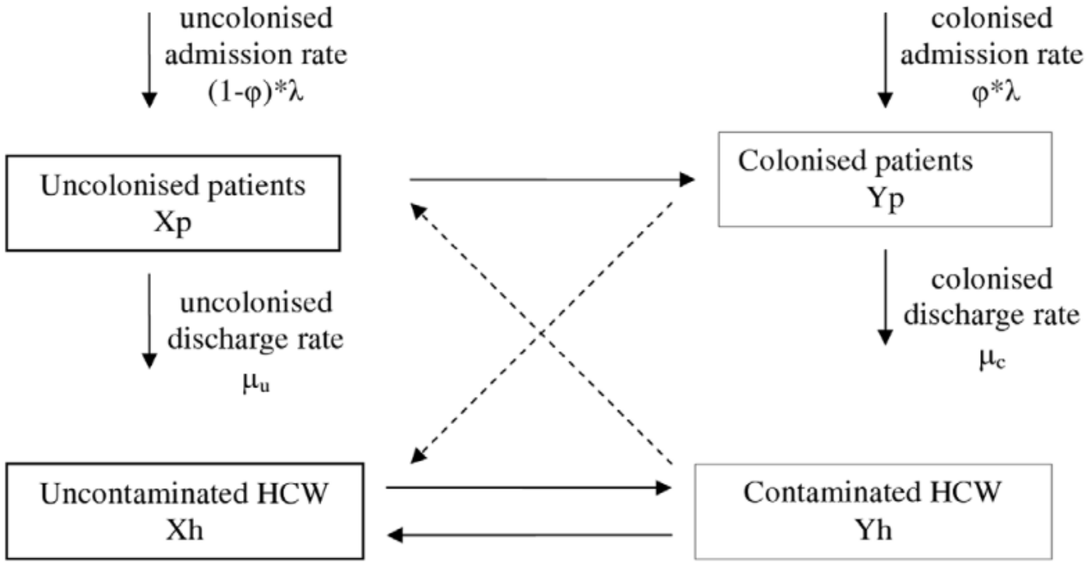
We report a case of lower urinary tract infection due to KPC-2-producing K. pneumoniae (KpCG02) in an elderly patient who had recently been hospitalized in Greece. The patient was treated successfully on an outpatient basis by removing the Foley catheter and with a prophylactic dose of gentamicin. KpCG02, which belonged to ST258, contained repFII plasmids that tested positive for the vagCD addiction system and the uge, wabG, urea, mrkD, and fimH virulence factors. This case reemphasizes the need for vigilance screening for carbapenem-resistant Gram negatives in patients with a history of travel to endemic areas, such as Greece.

Model of indirect transmission of CPKP between patients through health-care workers (HCWs) who act as vectors

Solid lines: movement to/from the four population groups
Dashed lines: transmission between patients and HCWs



Sypsa et al, 2012



R_0: the product of factors involved in the transmission from a colonized patient to a CPKP-free HCW (R_p) and from a contaminated HCW to a susceptible patient (R_h)

$$R_0 = R_p R_h = \frac{a^2 b_h b_p N_h N_p}{\mu_c \mu_h}$$

System of differential equations for the model

$$\frac{dX_p}{dt} = (1-\varphi)\lambda(\mathrm{B} - \mathrm{X_p} - \mathrm{Y_p}) \quad - \mu_u \mathrm{X_p} \quad - \alpha \mathrm{b_p X_p Y_h}$$

= uncolonizedpatients admitted - discharged

− becoming colonized during contact with contaminated HCW

$$\frac{dY_p}{dt} = \varphi\lambda(\mathrm{B} - \mathrm{X_p} - \mathrm{Y_p}) \quad - \mu_c \mathrm{Y_p} \quad + \alpha \mathrm{b_p X_p Y_h}$$

= colonized patients admitted - discharged

+ becoming colonized during contact with contaminated HCW

$$\frac{dX_h}{dt} = \mu_{hc} Y_h \quad - \alpha b_h Y_p X_h$$

= decontaminated HCWs - contaminated HCWs

$$\frac{dY_h}{dt} = -\frac{dX_h}{dt}$$

Sypsa et al, 2012

The impact of intervention measures in the transmission process

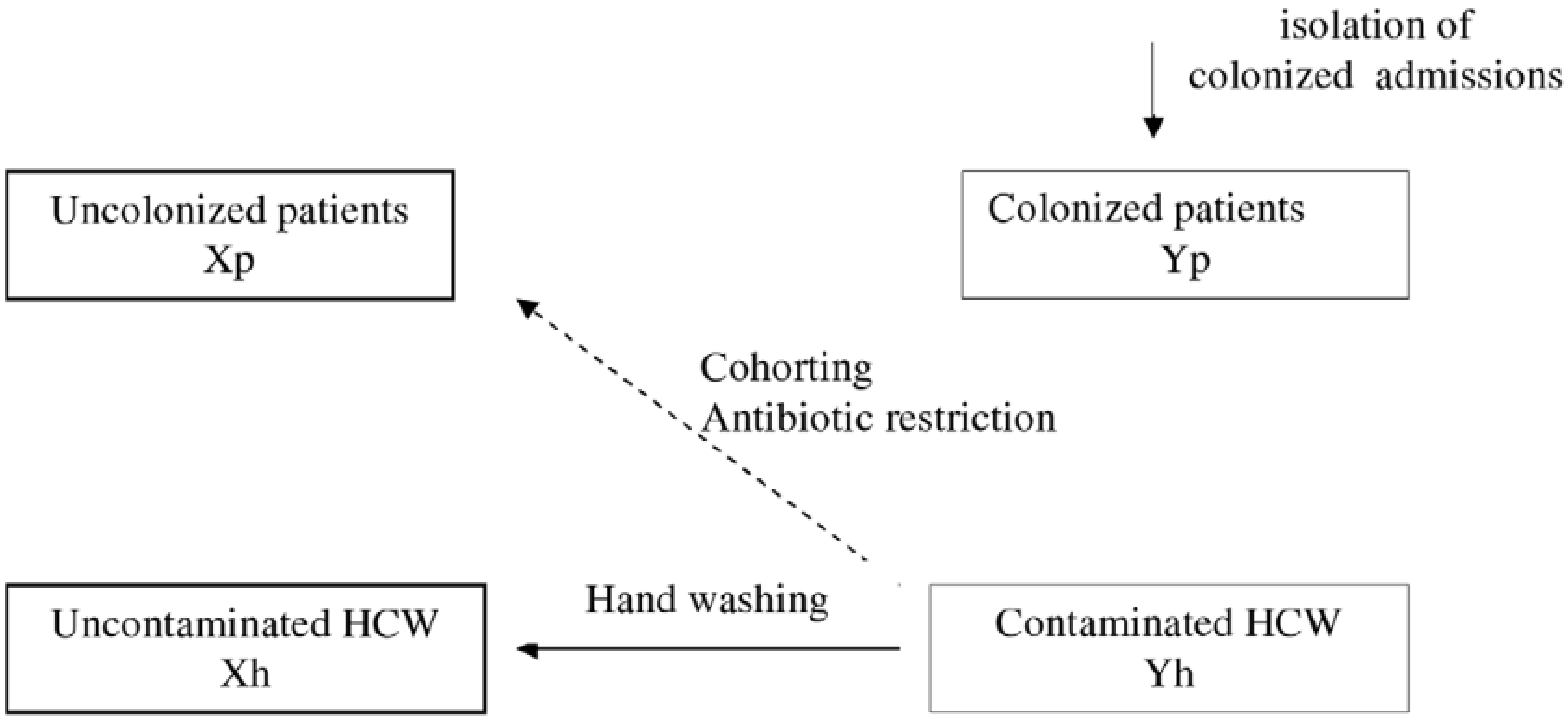
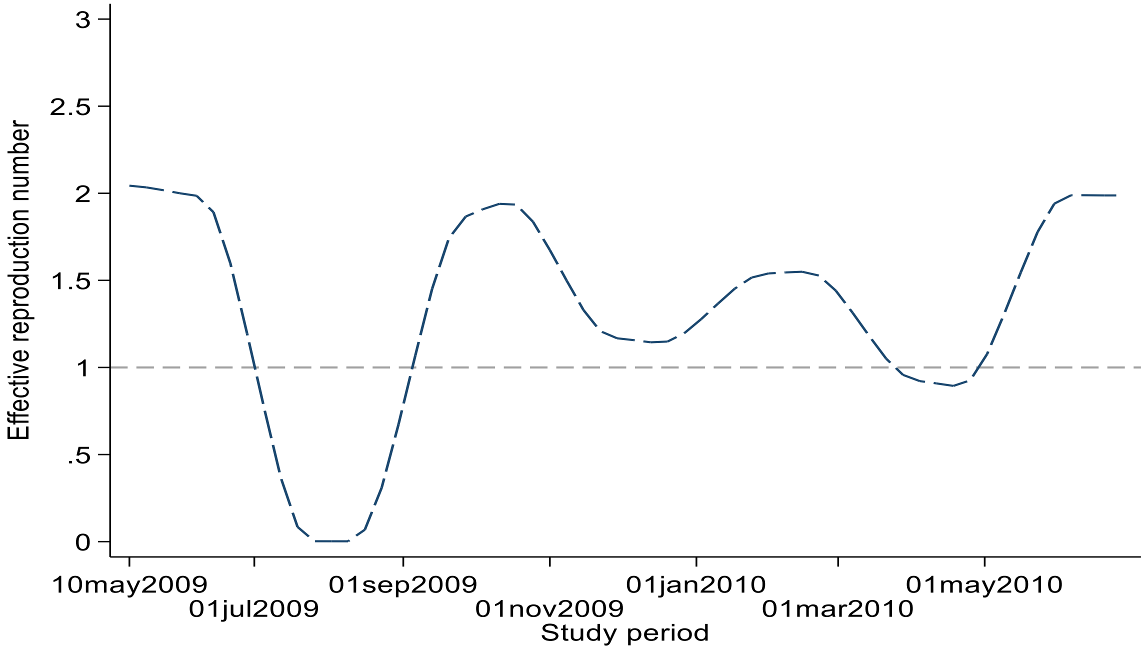


Table 1. Parameter estimates used in the model of CPKP transmission.

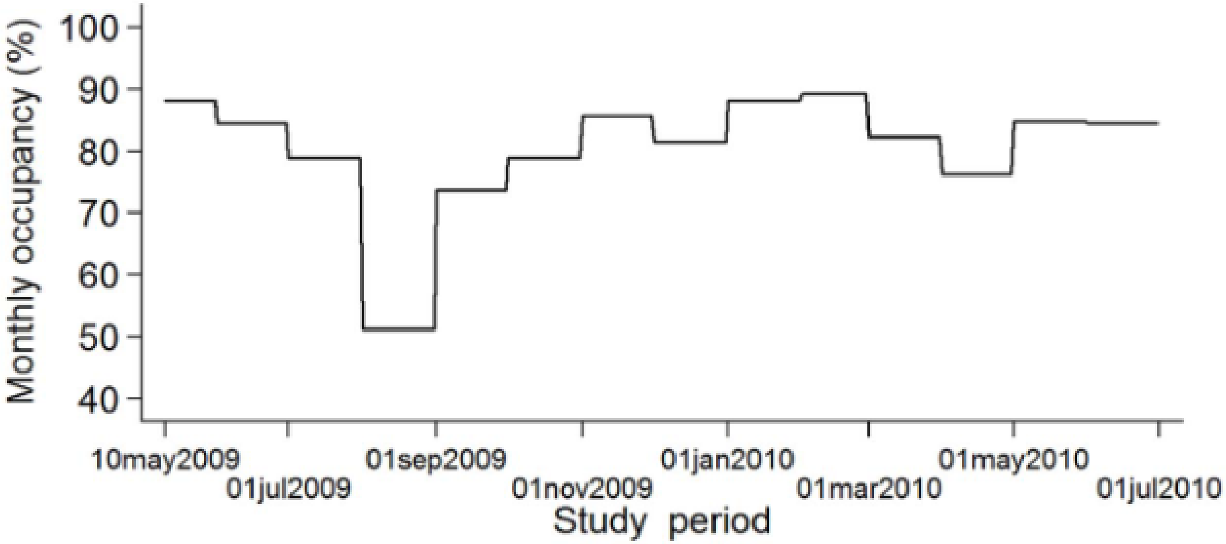
Parameter	Symbol	Value used in the model	Note
Number of beds	B	30	
Number of HCWs		24	Total daily number
Number of nursing staff		10	Total daily number
Discharge rate for uncolonized patients (/day)	μ_μ	1/10.3	1/duration of stay of uncolonized patients
Discharge rate for colonized patients (/day)	μ_c	1/22.9	1/duration of stay of colonized patients
Admission rate (/day)	λ	5.0–8.7	$\mu_u \frac{occupancy}{1-occupancy}$ using monthly estimates of bed occupancy
Colonization prevalence on admission (%)	φ	0%–4.9%	Monthly estimates
Per capita contact rate (/patient/HCW/day)	α	1.4	
Probability of a patient becoming colonized during contact with contaminated HCW	b_p	–	Estimated by the model
Probability of a HCW becoming contaminated during contact with colonized patient	b_h	21.4%	CPKP was isolated from the hands of HCWs in 15 out of 70 contacts with colonized patients
Decontamination rate of HCWs (/day)	μ_h	24	1/duration of contamination where duration is assumed 1 hour (1hour = 1/24 days)
Hand washing compliance	p	21%	

- The model was simulated stochastically assuming Poisson rates over small time steps for each of the seven events included in the model
- 1,000 simulations of the model were performed - the model was fit to the cumulative number of CPKP cases over time to estimate b_p

Sypsa et al, 2012

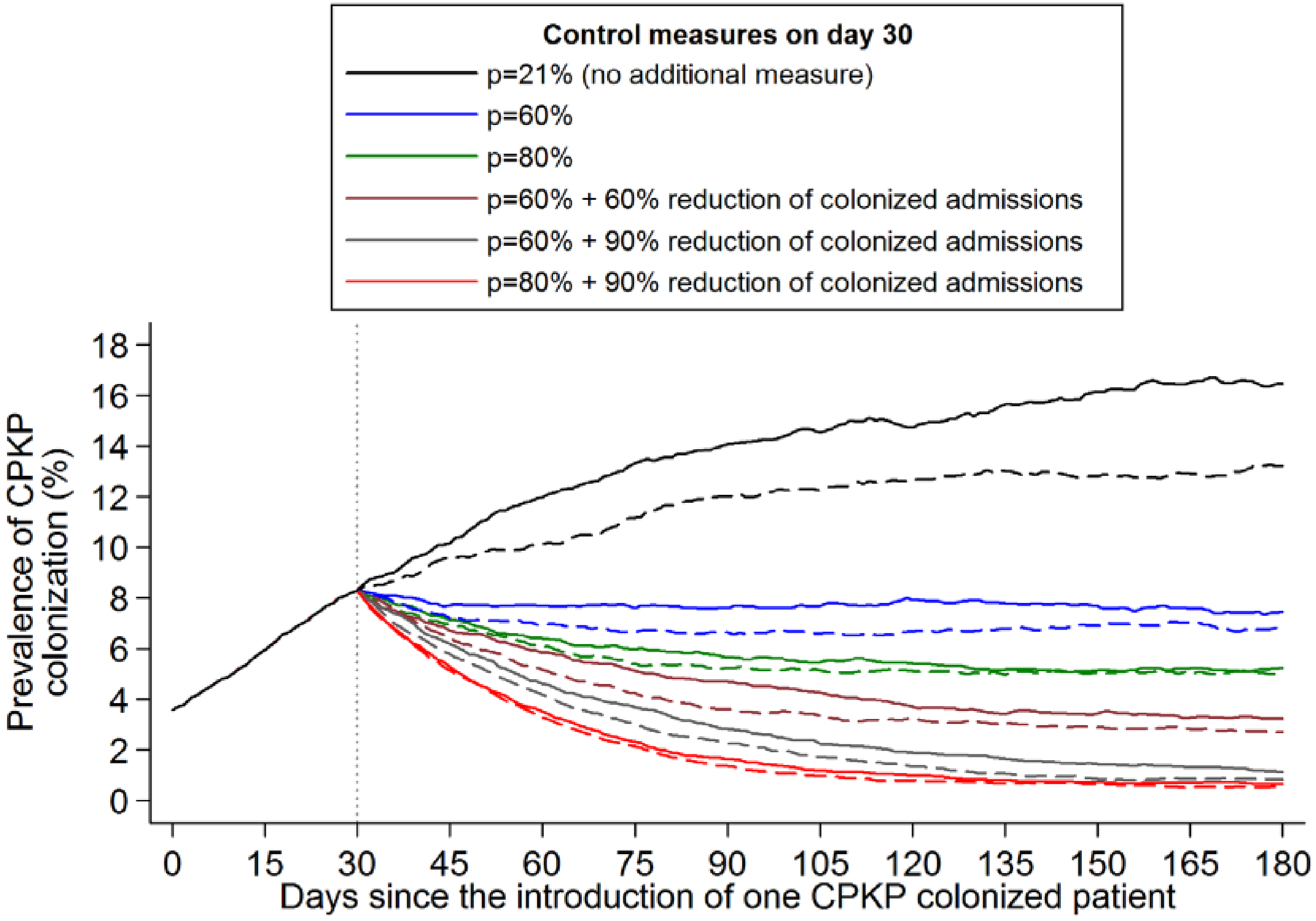


Bimonthly predicted **effective reproduction number R** (under the observed hand hygiene compliance rate of p = 21% during the study period)



Observed **occupancy** within the surgical unit during the study period (monthly estimates)

Impact of infection control measures on the prevalence of CPKP colonization

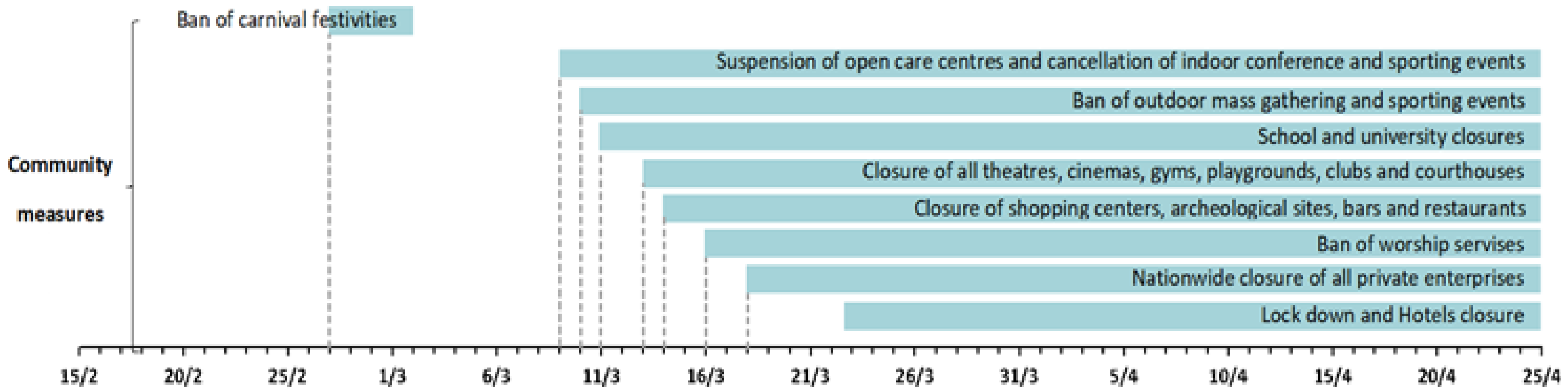


Dashed lines (- - -) correspond to the scenarios with the addition of 50% reduction in the duration of antibiotic usage during patients' stay in the unit (assuming a relative risk associated with antibiotic use equal to 3).

COVID-19 and social distancing measures

Assessing the impact of social distancing measures

Social distancing measures in Greece (1st wave of COVID-19)



Interesting questions:

What was the impact of these measures on transmission?

How can we disentangle the single effect of each measure?

Basic reproduction number R_0

Basic reproduction number $R_0 = \text{Max eigenvalue (G)}$

G: next generation matrix (g_{ij} → average number of secondary infections in age class i through the introduction of a single infectious individual of age class j into a fully susceptible population)

$$G = \frac{ND}{L}\beta$$

N: population size, D: mean duration of infectiousness, L: life expectancy

β the matrix of transmission rates β_{ij} at which an individual of age class *i* makes effective contact with a person of age class *j*

Relative change in R_0 resulting from the implementation of measures:

$$\frac{R_{0,2}}{R_{0,1}} = \frac{\text{Max eigenvalue } (\text{G}_2)}{\text{Max eigenvalue } (\text{G}_1)}$$

Assessing the impact of social distancing measures on transmission

Social contact hypothesis: Age-dependent transmission rates β_{ij} are directly proportional to the age-specific contact rates c_{ij} (Wallinga et al., 2006)

$$\boxed{\beta_{ij} = q \cdot c_{ij}}$$

q proportionality factor
(constant or may by e.g. age)

Let $\boldsymbol{C_1}$ and $\boldsymbol{C}_2$: social contact matrices without and with social distancing measures

→ **Relative change in R_0 resulting from these measures:**

$$\frac{R_{0,2}}{R_{0,1}} = \frac{\text{Max eigenvalue } (\frac{ND}{L} qC_2)}{\text{Max eigenvalue } (\frac{ND}{L} qC_1)} = \frac{\text{Max eigenvalue } (C_2)}{\text{Max eigenvalue } (C_1)}$$

Data on social contacts are needed

Collected from social contact surveys

- Contact diary for a 24-hour period
- Contact as either skin-to-skin contact or a 2-way conversation with >3 words spoken in the physical presence of another person.
- For each contact: information on the contact person’s age and location of the contact, such as home, school, workplace, transportation, leisure, or other

e.g.

Greece: social contacts were collected before and at different time points during the pandemic

UK: CoMix study

Disentangling the impact of social distancing measures (when multiple measures are applied)

e.g. Estimating the impact of school closure:

- Original matrix with social contacts reported on a regular weekday → C_1
- Synthetic contact matrix for school closure:

$$C_{school\ closure} = C_{home} + C_{work} + 0 \cdot C_{school} + C_{leisure} + C_{transportation} + C_{other}$$

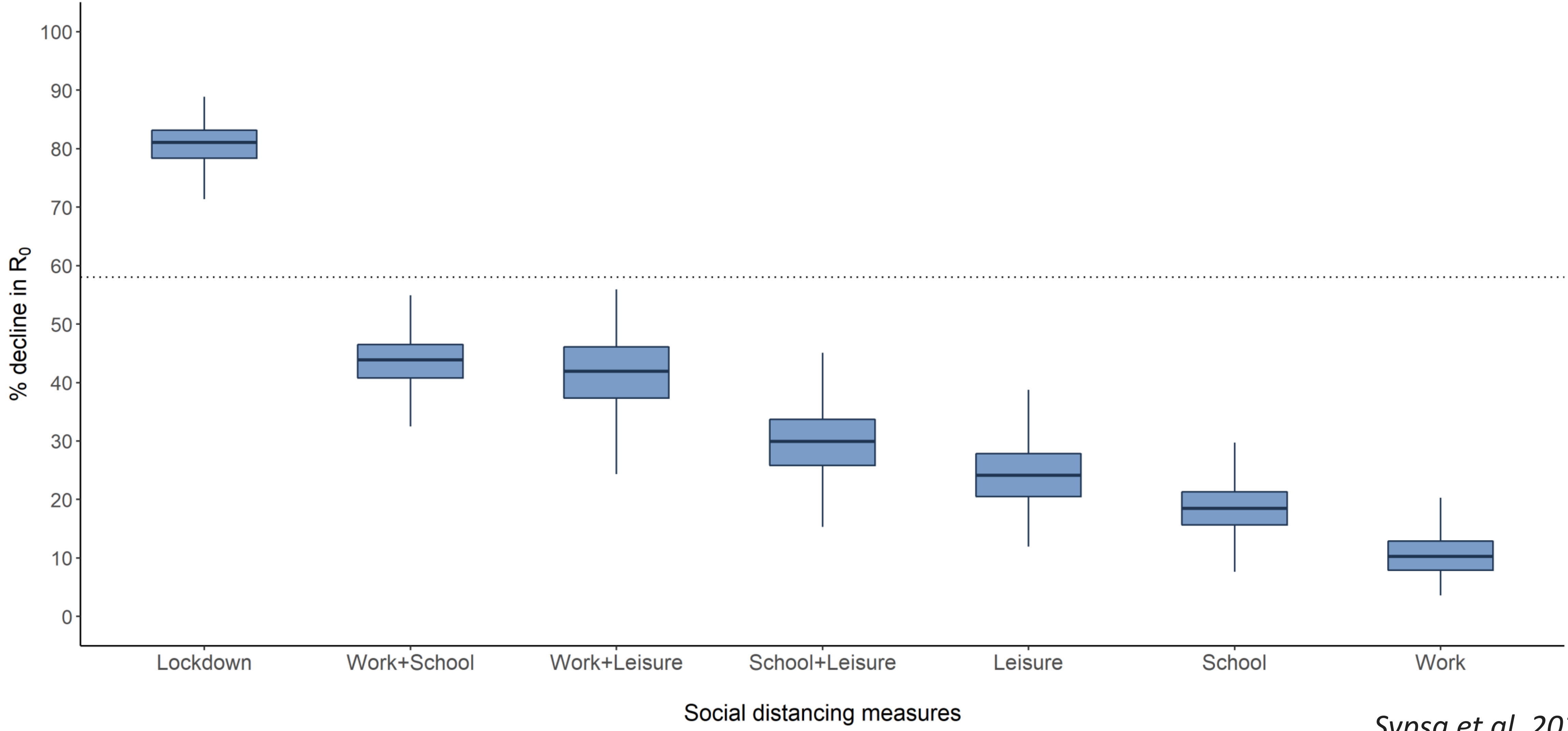
e.g. Estimating the impact of closing restaurants, coffee shops, cinemas etc. → leisure contacts data reduced by a proportion f

Synthetic contact matrix :

$$C_{reduction\ leisure} = C_{home} + C_{work} + C_{school} + (1 - f) \cdot C_{leisure} + C_{transportation} + C_{other}$$

- This approach can be used to assess the impact of combination of measures (e.g. school closure and reduction in contacts at work).

Assessing the impact of measures during the COVID-19 pandemic in Greece



Sypsa et al, 2020

Mixing patterns: bivariate smoothing

- Contact rates relevant to the spread of respiratory infections → mathematical modelling of infection dynamics
- Thus, we need empirical contact matrices built from social data

- Statistical estimation of contact rates by age from social contact data:

  The average number of contacts is modeled as a two-dimensional continuous function over age of respondent and contact, giving rise to a smooth “contact surface” (tensor-product spline derived from two smooth functions of the respondent’s and contact’s age, Goeyvaerts et al., 2010)

Age-mixing of the population

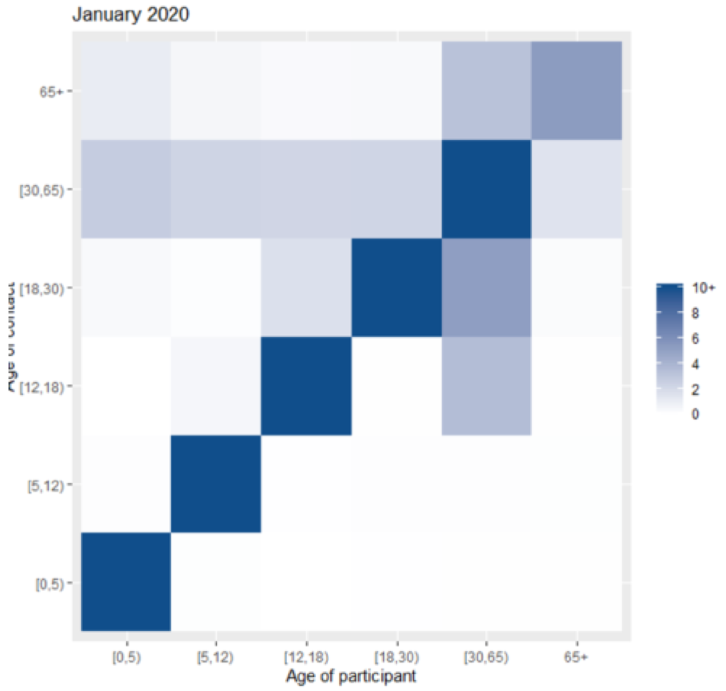
Define the number of age groups and build **age-specific contact matrices using data from social contact surveys**

Information can be extracted from self-reported contact diaries (e.g. Mossong et al, 2008)

socialmixr package, R software

Each cell represents the mean daily number of contacts that each member of an age group (row) has reported with members of the same or another age group (column).

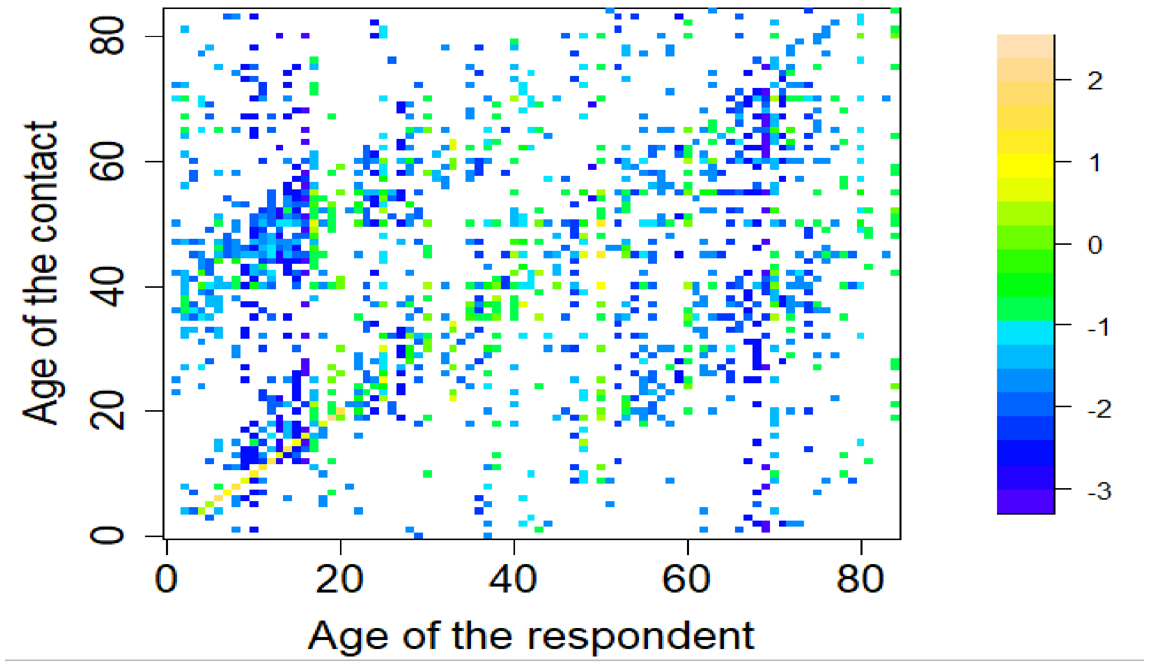
Social contact data from Greece, January 2020



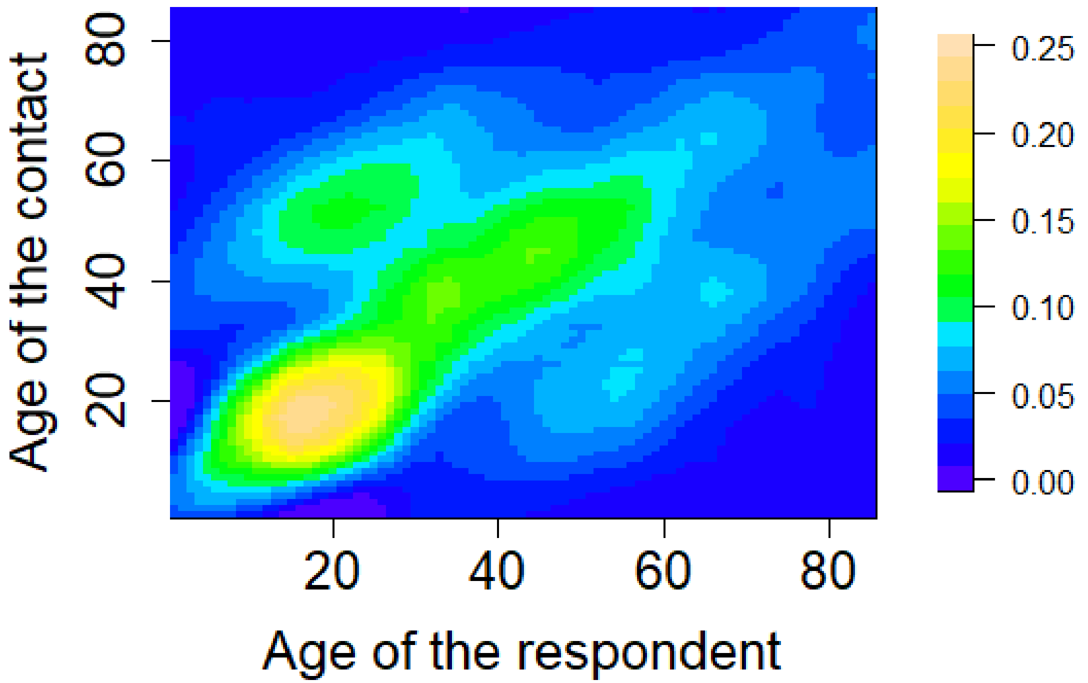
Sypsa et al, 2020

Bivariate smoothing of social contact data from Greece, January 2020

1-year observed log-contact rates



After bivariate smoothing



A white cell indicates that there were no contacts observed for those particular ages of the respondents and contacts.

A new smoothing constrained approach has been proposed (*Vandendijck et al, Biostatistics, 2023*)

Analysis of social contacts data in Greece: work in progress (Vasia Engeli, PhD student)

Closing remarks

Some examples were discussed here - many more interesting topics, e.g.

- the fading of mpox outbreak among MSM (depletion of susceptible MSM with high levels of sexual activity, Xiridou et al)

Infectious diseases are a fascinating topic for many different disciplines: infectious diseases specialists, (bio)statisticians, epidemiologists, sociologists etc.