Supplementary Information - Modelling antimicrobial resistance transmission to guide personalized antimicrobial stewardship interventions and infection control policies in healthcare setting: a pilot study.

Scoping review

Supplementary Table S1. Search terms used for the scoping review

Pathogen search terms:	"Enterobacteriaceae Infections"[Mesh] OR "Klebsiella Infections"[Mesh] OR "Klebsiella"[Mesh] OR "Klebsiella pneumoniae"[Mesh] OR "Carbapenem-Resistant Enterobacteriaceae"[Mesh] OR "Pseudomonas aeruginosa"[Mesh] OR "Pseudomonas Infections"[Mesh] OR "Acinetobacter baumannii"[Mesh] OR "Acinetobacter Infections"[Mesh] OR "Staphylococcal Infections"[Mesh] OR "Staphylococcus"[Mesh] OR "Staphylococcus aureus"[Mesh] OR "Methicillin-Resistant Staphylococcus aureus"[Mesh] OR "Enterococcus"[Mesh] OR "Vancomycin Resistance"[Mesh])
Intervention search terms:	"Cross Infection/prevention and control"[Mesh] OR "Health Facilities"[Mesh]) AND ("Bacterial Infections/prevention and control"[Mesh] OR "Bacterial Infections/drug therapy"[Mesh] OR "Anti-Bacterial Agents"[Mesh] OR "Drug Prescriptions/statistics and numerical data"[Mesh] OR "Behavior Therapy/methods"[Mesh] OR "Disinfectants/administration and dosage"[Mesh]) AND ("Cross Infection/transmission"[Mesh] OR "Drug Resistance, Microbial"[Mesh] OR "Drug Resistance, Multiple"[Mesh]

Supplementary Table S2. List of the retrieved variables from the systematic reviews

Variable	Description
Article	Title, first author
Year	Year
Article type	To clarify the type of article, e.g. systematic review, meta-analysis
Number of articles included	To clarify how many articles are included in the systematic review
Year data	Year/years to which data refer to
Setting	Type of setting from which data were
Interventions	Type of antimicrobial stewardship or infection control interventions
Pathogen	Resistant pathogens for which effectiveness of interventions were analysed
Parameters	Parameters utilized in the article to assess the intervention effectiveness, e.g. Incidence ratio (IR), odds ratio (OR), risk ratio (RR), risk difference (RD)
Impact of interventions	To clarify whether the impact of a specific intervention on a specific pathogen was calculated

Model

Supplementary Table S3. List of interventions and description of related model parameters

Cohorting	Cohorted contacts reduces HCW-patient mixing, by reducing the number of HCWs contributing to transmission [1]. In fact, if a fraction (q) of HCWs has cohorted contacts, the effective number of HCWs contributing to transmission is H(1-q), which was set in the model as the total HCW population (H_F+H_S+H_R).
Isolation and pre-emptive isolation	HCW-patient mixing can be decreased by reducing the number of daily contacts between HCWs and patients, through the respective parameter k_H.
Antibiotic consumption policies	By reducing the antibiotic DOTs or choosing antibiotics with lower risk of selecting resistant strains [1,2], it is possible to decrease the emergence and spread of resistant strains. In their study, Austin *et al* antibiotic restriction policies are introduced into the model to simulate reduction in selection pressure (and hence probability of patient colonization) [1]. They estimate that, if antibiotic selection pressure gives an increased relative risk ξ of acquisition whist the patient is receiving treatment, and patients receive antibiotics for a fraction ϵ of their LOS, then the probability per contact of colonization is increased by a factor of $A = 1 + \epsilon(\xi - 1)$. Within our case study, we estimate ϵ from the days of therapy (DOT) per pd of the resistance selecting antibiotics, as: $$\epsilon = \frac{avg.\,treatment\ duration}{LOS} = \frac{DOT\ per\ pd\ *\ pd\ /\ admitted\ patients}{LOS} = \frac{DOT\ per\ pd\ *\ LOS}{LOS} = DOT\ per\ pd = 0.231$$ where the average treatment duration is meant to be as if the daily doses observed had been distributed to all the patients admitted, thus it must not be confused with the average treatment duration calculated only on the patients who received an antibiotic treatment. The increased relative risk estimate is $\xi = 3.15$, as the average of the resistance selecting antibiotics increased risks from [6]. The average is computed on literature risks weighted on hospital data DOTs of β-lactam, cephalosporins, carbapenems and fluoroquinolones antibiotics. Antibiotic prescription for the patients was considered as independent from the

	epidemiological status, in the sense that the DOTs were considered to be the same for each epidemiological compartment (P_F, P_S, P_R).
Hand hygiene	Hand hygiene compliance reduces the probability of bacterial transmission during the contacts between contaminated and un-colonized individuals [3]. Data on sanitizing gel (containing at least the 60% of ethanol) consumptions can be used as a proxy for hand hygiene compliance. In particular, the following equations are consistent with our mathematical model: $$C_h = \#\ of\ contacts\ followed\ by\ sanitization = gel\ consumption\ per\ pd\ *\ pd\ /\ single\ gel\ dose$$ $$C = \#\ of\ contacts = K_H * H * pd$$ $$h = \frac{\#\ of\ contacts\ followed\ by\ sanitizations}{\#\ of\ contacts} = \frac{gel\ consumption\ per\ pd\ /\ single\ gel\ dose}{K_H * H}$$ where the gel consumption (0.04427 litres per patient-days) and the number H=17 of HCWs were obtained from the SAVE data, while the recommended single sanitizing hand gel dose (0.004 litres) is indicated in the WHO Guidelines on Hand Hygiene in Health Care. From these equations, we can extract the constrained relationship between hand washing probability and daily contact rate, and use it to remove one free parameter. In our study, we a priori estimated a contact value of $k_H = \frac{7.3\ \text{contacts per patient}}{\text{H}} = 1.39$ contacts per patient per HCW, where the number of daily contacts per patient was calculated as the weighted average between the contact rate used in for surgery HCWs and the rate observed in or the ICU [3,4]. The hand washing probability thus resulted $h = 0.675$, which has been used as initial value for the fit.
Screening at admission	Universal screening was modelled through the parameter describing the resistance prevalence at admission as it usually results in patient isolation thus decreasing the entry of individuals colonized/infected with resistant strains. The fraction of patients colonized and or infected at admission had been extracted from the hospital data. To simulate the effect of the screening at admission, followed by isolation, we decreased or increased this rate of infected people at admission.

Supplementary Table S4. Interventions and their impact on model parameters.

Intervention	**Impact on model**
Cohorting [1]	*H -> (1-q)H*
Isolation and pre-emptive isolation [3]	k_h
Antibiotic consumption policies [2]	$A = 1 + \varepsilon(\xi - 1)$
Hand hygiene [3]	h
Screening at admission (see Table 3)	p_R

Clinical data (SAVE intervention)

To estimate KP prevalence only samples collected within the 72 hours from admission were selected. The samples comprised rectal swabs from screening activities and clinical specimens from different sources collected at the discretion of the attending physicians (e.g. blood, wound swabs, urine, sputum, bronchoalveolar lavage). Patients colonized and/or infected by resistant strain were defined as those with a sample positive for CRKP; patients colonized and/or infected by sensitive strain (CSKP) were defined as those with a negative result for CRKP (*e.g.* samples of *Klebsiella pneumoniae* ESBL-producers were considered in this category); uncolonized or "free" patients were defined as those with negative microbiological samples or positive for pathogens other than *K. pneumoniae*. AMC data (including defined daily dose-DDD and days of therapy-DOT) were collected for a list of antibiotics for which exposure has been associated with the development of the carbapenem-resistance: carbapenems (ertapenem, meropenem, imipenem/cilastatin), betalactams-betalactamases inhibitors combinations (BLBLI) (amoxicillin-clavulanate and piperacillin-tazobactam), third and fourth generation cephalosporins (ceftazidime, ceftriaxone, and cefepime), and fluoroquinolones (ciprofloxacin and levofloxacin) [2]. Bed occupancy, number of admissions, length of hospital stay, staffing (nurses) levels were also recorded (Tables 5, 6, 7).

Supplementary Table S5. a) Variables collected for model validation. AMC: antimicrobial consumption; DDD: defined daily dose; DOT: days of therapy; HCW: health care worker; PF: not

colonized/free; PR: colonized/infectd by resistant strain; PS: colonized/infected by susceptible strain. b) DOTs per patient-day for the different antibiotic classes.

(a)

Variable	**Description**
Prevalence on admission	Percentage of colonized/infected patients (S and R) at admission
Weekly point prevalence	Percentage of colonized/infected (S and R) patients hospitalized at time of data collection
Number of beds	Number of beds available in the ward considered
Length of stay for P_F- P_S- P_R	Average days spent in the hospital by patients
HCW to patient ratio	Number of HCW in relation to the number of patients.
Patient days	Total number of days spent by patients in the hospital
Number of admissions	Total number of patients hospitalized in the time period considered
AMC data	DDDs and DOTs of antibiotics associated to carbapenem-resistance development

(b)

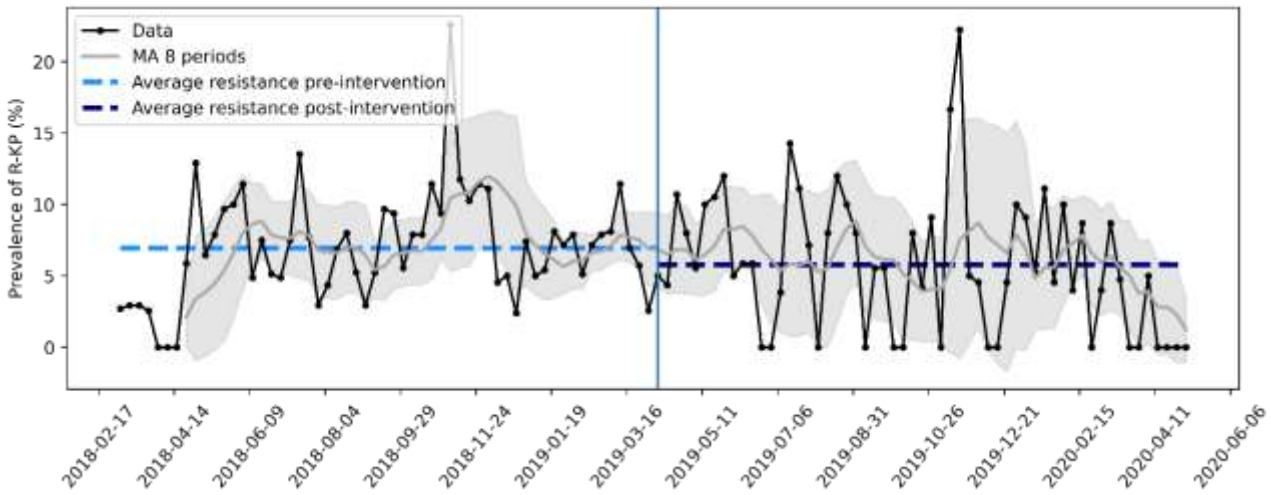
Antibiotic class	DOTs per pd pre-intervention	DOTs per pd post-intervention
Penicillins	100.46	90.23
Cephalosporins	47.66	28.87
Carbapenems	61.05	19.93
Fluoroquinolones	21.64	6.48

Supplementary Table S6. Summary of SAVE data from pre and post-intevention periods. CSKP:arbapenem-susceptible Klebsiella pneumoniae; CRKP:c arbapenem-resistant Klebsiella pneumoniae; DOT:; KP: Klebsiella penumoniae.

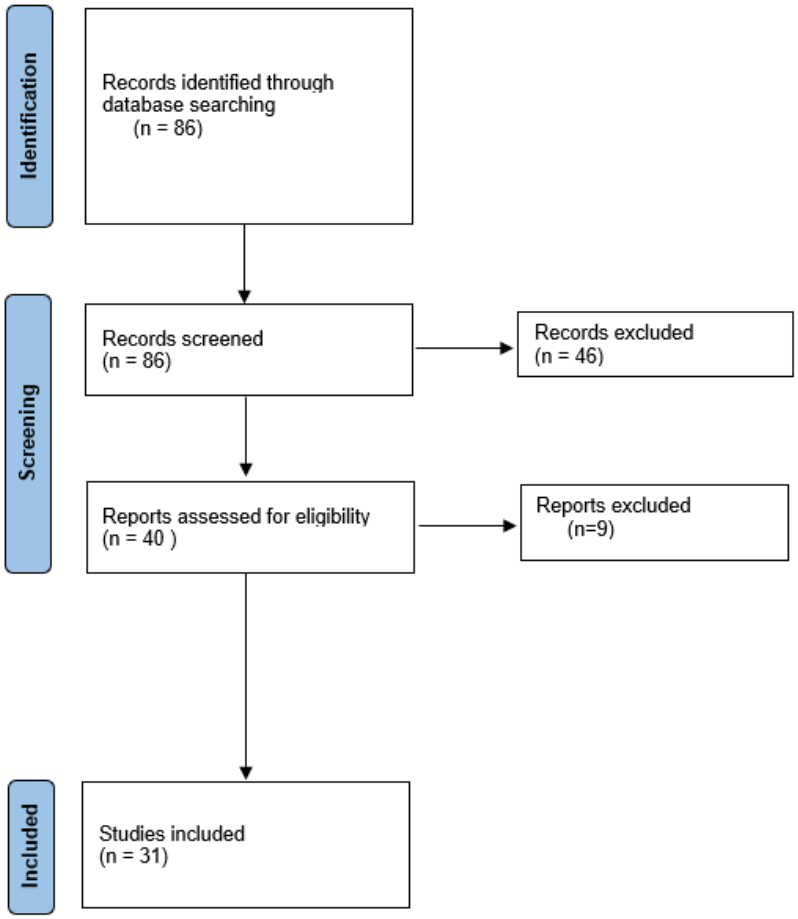
Variables	**Pre-intervention N (%)**	**Post-intervention N (%)**
Prevalence on admission		
Total isolates (<72h from admission)	883 (100%)	223 (100%)
CSKP	22 (2.5%)	3 (1.3%)
CRKP	5 (0.6%)	16 (7.2%)
Free KP	856 (96.9%)	204 (91.5%)
Weekly point prevalence	**Pre-intervention (N)**	**Post-intervention (N)**
CSKP	117	62
CRKP	139	69
Free KP	1760	1061
CRKP prevalence	7.0%	5.8%
Mean CRKP/week	2.4	1.2
Length of stay	**Pre-intervention days (d)**	**Post-intervention days (d)**
CSKP	32.4 d	34 d

CRKP	60 d	45 d
Free KP	10,05 d	8,69 d
Ward data	**Pre-intervention (N)**	**Post-intervention (N)**
Number of beds	46	46
Number of nurses/patient ratio	6,2	6,2
Bed occupancy	79%	71%
Admissions	1357	1421
Patient days	14382	13008
Total consumption of alcohol gel	357,6	446,9
Alcohol gel consumption per 1000 patient days	24,19	34,36
Antibiotic consumption DOT per 1000pd	231	146

Supplementary Figure S1. CRKP weekly point prevalence over time, plotted both as raw data and as a moving average on 8 periods-weeks with the standard deviation as confidence interval. Dashed lines represent the average resistance prevalence before (light blue) and after (dark blue) the intervention



Supplementary Figure S2. Flow chart of the scoping review

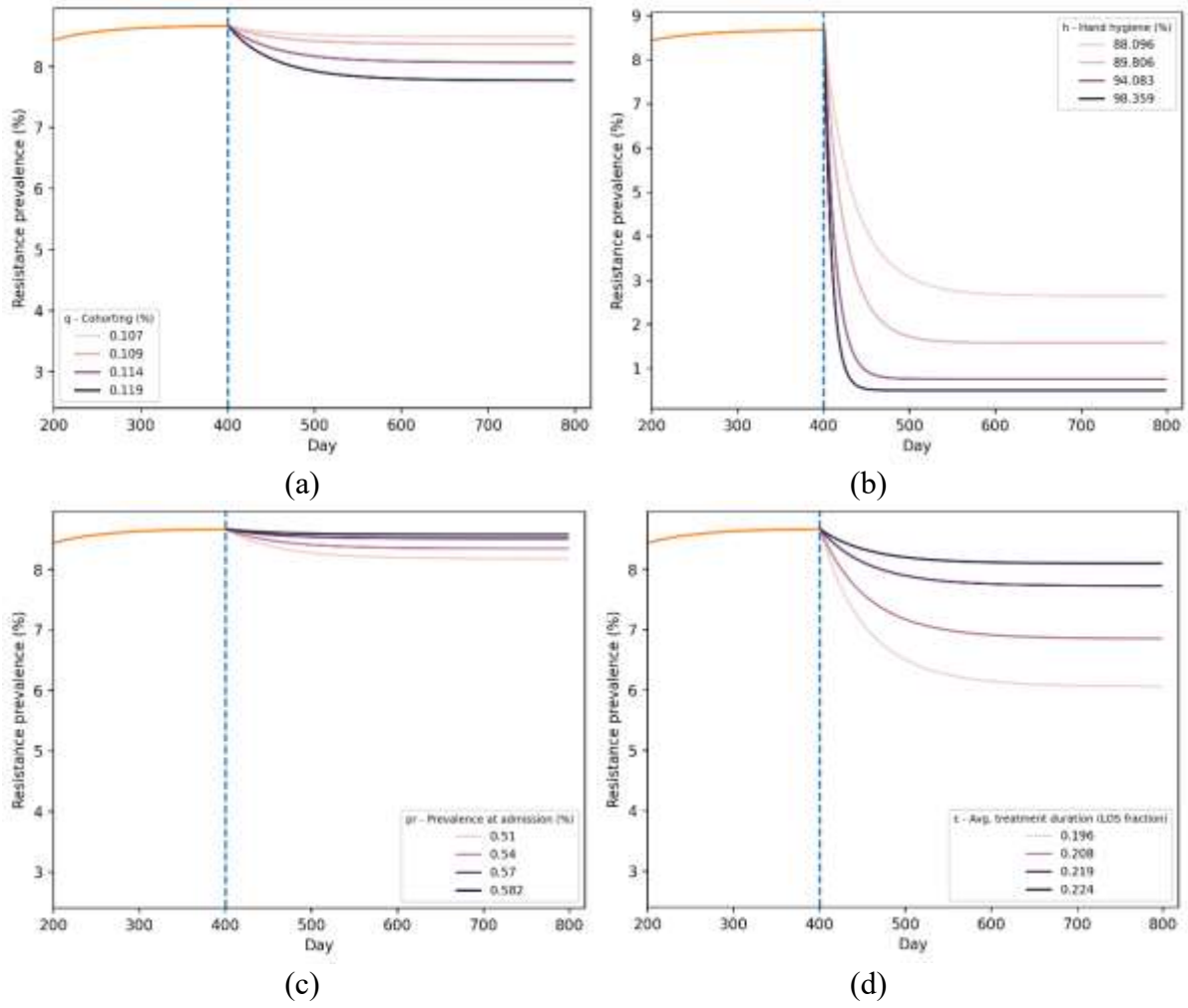


Supplementary Table S7. List of publications analysing the impact of Infection Prevention and control (IPC) or Antibiotic stewardship (AMS) interventions included in this study. SR: systematic review; MA: meta-analysis; LTCF: Long-term care facilities; MRSA: Methicillin-resistant Staphylococcus aureus; MDRO: Multidrug-resistant organisms; Vancomycin-resistant Enterococci (VRE); CDI: Clostridium difficile infection; CRE: Carbapenem-resistant Enterobacterales; CRAB: Carbapenem-resistant Acinetobacter baumannii; CRPA: Carbapenem-resistant Pseudomonas aeruginosa; DDD: defined daily dose; ESBL: Extended spectrum beta-lactamase; NA: Not available; Trend: Range of change in slope of the outcome between pre- and post-intervention; IC: Immediate change in the level of outcome between pre- and post-intervention; LOS: Length of stay; RR: Pooled risk ratio, reduction in colonization and/or infection rate after intervention; RaRa: Pooled rate ratio, rate ratio of infections and/or colonisation between standard of care and intervention period; IRaRa: Incidence rate ratio, incidence rate ratio of infections and/or colonisation between standard of care and intervention; IRs: Incidence ratio, ratio between infection/colonisation before and after intervention; %r: Percentage of reduction, reduction expressed in percentage of specific infection caused by a specific pathogen; IRD: Incidence rate difference, difference in incidence rate per 1000 patient days of resistant bacteria; OR: odds ratio, change in incidence of infection and/or colonisation.

First author Year of publication	Study type	Setting	Intervention	Pathogen	Parameters	Other outcomes
Tomczyk S. 2019 [5]	SR	Healthcare	IPC	CRE, CRAB, CRPA	Trend, IC	
Lee M.H. 2019 [6]	SR	LTCF	IPC	MDRO	Descriptive	
Fan C.Y. 2019 [7]	MA	Hospital	IPC	CRAB	RR	
Chang N.C.N. 2019 [8]	SR, MA	Healthcare	IPC	MRSA, VRE	IRaRa	CDI
Nathwani D. 2019 [9]	SR	Hospital	AMS	MDRO	Descriptive	LOS, mortality, costs
Bertollo L.G. 2018 [10]	SR	Hospital	AMS	MDRO	Descriptive	LOS, mortality, DDD, costs, CDI
Moralejo D. 2018 [11]	SR	Healthcare	IPC	MRSA	Descriptive	
Baur D. 2017 [12]	SR, MA	Hospital	AMS	MRSA, VRE, ESBL	IRs	CDI
Davey P. 2017 [13]	SR, MA	Hospital	AMS	MDRO	RD	LOS, CDI
Teerawattanapong 2017 [14]	SR, MA	Hospital	IPC and AMS	ESBL, CRE, CRAB, CRPA	RaRa	Mortality
Honda H. 2017 [15]	SR, MA	Healthcare	AMS	MRSA, ESBL, CRAB, CRPA	ARD	LOS, mortality, DDD, costs
Marra A.R. 2017 [16]	SR, MA	Hospital	IPC	MRSA, VRE	RR	CDI
Van Dijck C. 2017 [17]	SR	Hospital	AMS	MDRO	Descriptive	Mortality, DDD
Kizny Gordon A.E. 2017 [18]	SR	Healthcare	IPC	CRE, CRAB, CRPA	Descriptive	

Gould D.J. 2017 [19]	SR, MA	Healthcare	IPC	MRSA	Descriptive	
Karanika S. 2016 [20]	SR, MA	Hospital	AMS	MRSA, ESBL, CRPA	%c, RD	LOS, Mortality, DDD, CDI
Nair R. 2016 [21]	SR, MA	Healthcare	IPC	MRSA	RR	Mortality
Frost S.A. 2016 [22]	SR, MA	Hospital	IPC	MRSA, VRE	IRR	CDI
Schuts E.C. 2016 [23]	SR, MA	Healthcare	AMS	MDRO	Descriptive	LOS, mortality, costs, nephrotoxicity
Campos A.C. 2016 [24]	SR	Healthcare	IPC and AMS	CRKP	Descriptive	
Kim H.Y. 2015 [25]	MA	Hospital	IPC	MRSA, VRE	RR	
Zaky A. 2015 [26]	SR	Hospital	IPC and AMS	MDRO	OR	LOS, mortality
López-Alcalde J. 2015 [27]	SR	Hospital	IPC	MRSA	na	
De Angelis G. 2014 [28]	SR, MA	Hospital	IPC	VRE	RR	LOS, mortality, costs
zur Wiesch P.A. 2014 [29]	SR, MA	Hospital	AMS	MDRO	IRD	
Kock R. 2014 [30]	SR	Hospital	IPC	MRSA	Descriptive	
Daneman N. 2013 [31]	SR, MA	Hospital	IPC	MRSA, VRE, ESBL	OR	
Hughes C. 2013 [32]	SR	LTCF	IPC	MRSA	na	
Chen A.F. 2013 [33]	SR	Hospital	IPC	MRSA	%r	Costs
Karki S. 2012 [34]	SR, MA	Healthcare	IPC	MRSA, VRE	IRaRa	
Kaki R. 2011 [35]	SR	Hospital	AMS	MRSA, ESBL	Descriptive	DDD, costs

Supplementary Figure S3. Model predictions of CRKP prevalence over time (% of resistant patients w.r.t. total) when implementing interventions. Before day 400 is the pre-intervention period. After day 400, multiple scenarios are simulated corresponding to stricter interventions (3%, 5%, 10%, 15% stricter than the initial value). a) Cohorting level, b) hand hygiene, c) screening at admission aimed to reduce prevalence at admission, d) antibiotic restriction policies aimed to reduce treatment duration.



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