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A One-Health quantitative model to assess the risk of antibiotic resistance acquisition in Asian populations: impact of exposure through food, water, livestock and humans

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Abstract

Antimicrobial resistance (AMR) has become a major threat worldwide, especially in countries with inadequate sanitation and low antibiotic regulation. However, adequately prioritizing AMR interventions in such settings requires a quantification of the relative impacts of environmental, animal, and human sources in a One-Health perspective. Here, we propose a stochastic quantitative risk assessment model for the different components at interplay in AMR selection and spread. The model computes the incidence of AMR colonization in humans from five different sources: water or food consumption, contacts with livestock, and inter-human contacts in hospitals or the community, and combines these incidences into a per-year acquisition risk. Using data from the literature and Monte-Carlo simulations, we apply the model to hypothetical Asian-like settings, focusing on resistant bacteria that may cause infections in humans. In both scenarios A, illustrative of low-income countries, and B, illustrative of high-income countries, the overall individual risk of becoming colonized with resistant bacteria at least once per year is high. However, the average predicted incidence of colonization was lower in scenario B at 0.82 (CrI [0.13,5.1]) acquisitions/person/year, *vs* 1.69 (CrI [0.66, 11.13]) acquisitions/person/year for scenario A. A high percentage of population with no access to improved water on premises and a high percentage of population involved in husbandry are shown to strongly increase the AMR acquisition risk. The One-Health AMR risk assessment framework we developed may prove useful to policy makers throughout Asia, as it can easily be parameterized to realistically reproduce conditions in a given country, provided data is available.

KEY WORDS: health risk assessment; exposure assessment; antibiotic resistance; One-Health; Asia; Monte-Carlo simulation; acquisition; transmission

Summary for social media

Antimicrobial resistance has become a major threat worldwide, especially in countries with inadequate sanitation and low antibiotic regulation. However, adequately prioritizing interventions against resistance requires a quantification of the relative impacts of environmental, animal, and human sources in a One-Health perspective. In this work, we propose a framework to quantitatively assess the risk of resistance acquisition in human populations, accounting for five different sources: water or food consumption, contacts with livestock, and inter-human contacts in hospitals or the community. Using data from the literature and computer simulations, we apply the model to hypothetical Asian-like settings, focusing on resistant bacteria that may cause infections in humans. Our results suggest that the risk of resistance acquisition could be twice higher in typical low-income Asian countries than in high-income Asian countries. A high percentage of population with no access to improved water on premises and a high percentage of population involved in husbandry are shown to strongly increase this risk. We hope that the One-Health risk assessment framework we developed may prove useful to policy makers throughout Asia, as it can easily be parameterized to realistically reproduce conditions in a given country, provided data is available.

1. INTRODUCTION

Antibiotics are regarded as one of the most significant medical achievements of the 20th century. However, systematic misuse and overuse of these drugs in human medicine and food production has accelerated the development of antimicrobial resistance (AMR), threatening the sustainability of an effective global public health response to infectious diseases (Davies & Davies, 2010; WHO, 2014). Harmonized and immediate actions on a global scale are needed to mitigate AMR burden and prioritization of AMR control interventions is essential for optimal allocation of risk management attention, particularly in resource-limited settings. In South and Southeast Asia, which incur high burdens of bacterial diseases and where most of the drivers of AMR emergence and spread are found (WHO, 2019), few systematic studies have been conducted to allow prioritization of control interventions.

The emergence and spread of antibiotic-resistant bacteria (ARB) are not only the consequences of biological mechanisms; they also involve policies, economics, socio-cultural beliefs, and behaviors as well as awareness on antimicrobial stewardship and AMR containment and occur in three primary and interdependent sectors: the human sector, the animal sector, and the environment (Hernando-Amado, Coque, Baquero, & Martinez, 2019). In Asia, given the complexity and extent of AMR, resources are often insufficient to address all concerns. Moreover, knowledge on the AMR situation is often poor. At the state or regional level, quantities of antibiotics consumed or prevalence of resistance in waters or food products may for example be unknown or not well documented. To what extent would a modification of practices in terms of antibiotic usage in humans or in livestock affect the risk of antibiotic resistance acquisition in humans? How do hygiene and sanitation levels affect that risk? It is essential to scientifically assess how different factors impact AMR risk in populations to be able to prioritize AMR control interventions (Nadimpalli et al., 2018; WHO, 2019).

In a previous work, a situational analysis of AMR status in WHO's South-East Asian countries was performed using a risk assessment approach based on a systematic

description of processes at play in the acquisition, selection, and spread of ARB in the specific context of South-East Asia (Chereau, Opatowski, Tourdjman, & Vong, 2017). This approach helped identify gaps in critical knowledge and weaknesses in the relevant infrastructures and underlined the importance of developing a coordinated One-Health strategy to contain AMR in South-East Asia. However, the assessment performed was only qualitative. The development of a quantitative (or semi-quantitative) risk assessment model using computational tools is a further step that can allow working with scenarios with varying settings and quality of interventions and subsequent calculations of risks.

Quantitative risk assessment has proven useful in the last decades to assess the level of threat for human health associated with ARB coming from livestock animals exposed to antibiotics (Anderson, Woo, & Crawford, 2001; Cox, 2005; Cox & Popken, 2004, 2014; Hurd et al., 2004; Kelly et al., 2004; Singer et al., 2007), as well as the level of human exposure to AMR through bathing water or food consumption (Alban, Ellis-Iversen, Andreasen, Dahl, & Sonksen, 2017; Ben et al., 2019; Evers et al., 2017; O'Flaherty, Solimini, Pantanella, & Cummins, 2019; Sun et al., 2016), with the potential to facilitate the selection of the most appropriate interventions in a complex situation.

We propose here a One-Health quantitative risk assessment model that computes numerical estimates of the incidence of AMR colonization in humans from 5 different sources: water or food consumption, contacts with livestock, and inter-human contacts in hospitals and the community, and combines these incidences into an individual per-year acquisition risk. We run the model for two different settings illustrative of Asian countries, including one well-developed country (high middle-income country or high-income country) and one developing country (low middle-income country).

2. METHODS

2.1. General AMR model

2.1.1 Definitions and Hypotheses

We built a conceptual risk assessment model that provides an overall picture of the selection and spread of an ARB within a country. The three major components classically considered when taking a One-Health approach on ARB acquisition in humans have been included in the model: human transmission, animal-to-human transmission, and environment-to-human transmission. The model was deliberately built to be generic. It depicts the selection and spread of any resistant bacterial species, that could typically be carried asymptomatically in humans but with clinical relevance - that is, with a pathogenic potential -, such as methicillin-resistant *Staphylococcus aureus* or extended-spectrum beta-lactamase producing *Enterobacteriaceae*.

Hazard identification (identifying situations where acquisition of resistant pathogens may occur) and exposure assessment (quantifying amounts of exposure during these situations) were used to develop a hierarchical model outlining key-steps in the pathways driving the spread of antibiotic resistance within and between the three major components.

The likelihood of occurrence of each key-step was parameterized based on context assessment data. Context-driven factors for each component include level of surveillance, antibiotic stewardship in humans and animals, infection control, and prevention.

Parameters. The model includes two sets of parameters (inputs): a list of parameters related to the mechanistic processes; and a list of situational parameters, associated with the drivers, the impact of interventions, and the frequency of interventions implementation in the studied countries.

2.1.2 Model

The overall model of ARB acquisition is composed of five sub-models predicting the acquisition of an ARB via water or food consumption, contacts with livestock, and inter-human contacts in hospitals or the community. The hierarchical structure of this overall model is depicted by the schematic on Fig. 1.

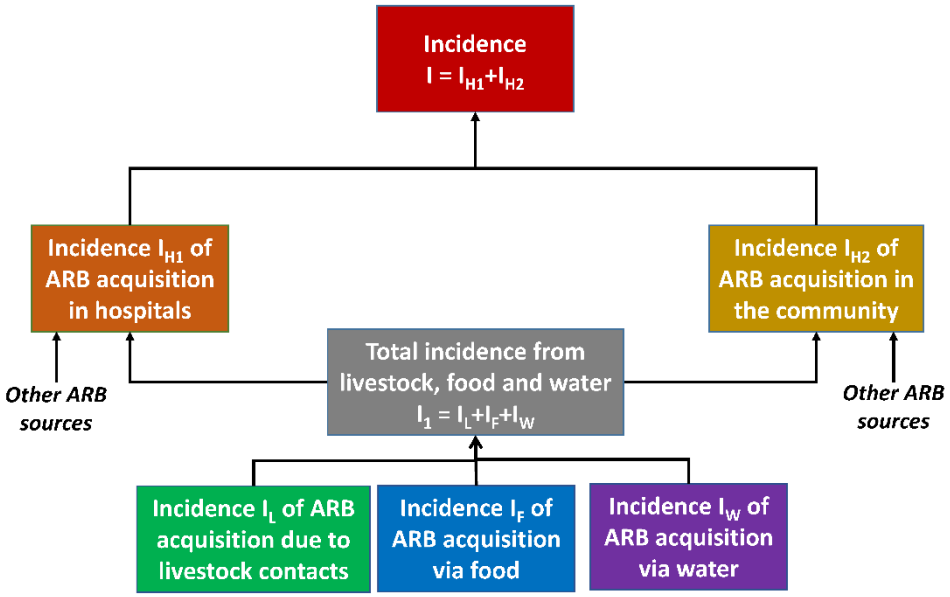


Fig. 1. Overall model of ARB acquisition risk. The model accounts for 5 reservoirs of ARB: livestock, food, water, hospitals and the general population. The 1-year incidences of acquisition of the ARB are computed for each of these reservoirs and put together to compute a global acquisition risk.

For each of these sub-models, the output is the 1-year incidence rate of acquisition of the ARB per 100 individuals via the corresponding route of acquisition, defined as the number of new acquisitions with the ARB from this route, per 100 individuals over one year. The overall 1-year incidence **I** of acquisition of the ARB per 100 individuals may then be computed from the outputs $\mathbf{I_L}$ (livestock-associated incidence), $\mathbf{I_F}$ (food-associated incidence), $\mathbf{I_W}$ (water-associated incidence), $\mathbf{I_{H1}}$ (community-associated incidence), and $\mathbf{I_{H2}}$ (hospital-associated incidence) of the five sub-models as follows.

(a) The 1-year incidence $\mathbf{I_1}$ of acquisition of the ARB per 100 individuals (number of acquisitions per 100 individuals per year) due to their general surroundings and living conditions, including livestock contacts, food consumption, and water consumption, may be computed as:

$$\mathbf{I_1} = \mathbf{I_L} + \mathbf{I_F} + \mathbf{I_W} \quad \text{(eq. 1)}$$

(b) Let **D** be the average duration of carriage of the considered ARB, in years. **D** needs to be calibrated from the literature for each ARB species. Here we assume that **D** follows a Gaussian distribution with an 8-day mean, mostly reflecting short-term ARB carriage after contamination in healthy individuals, as seen for instance in multi-resistant Enterobacteriaceae (OstholmBalkhed et al., 2018):

$$\mathbf{D} \sim \text{Normal}(8/365;0.01) \qquad \text{(eq. 2)}$$

(c) Then, the average community prevalence (**P1**) of carriage of the ARB may be computed, assuming that it is stable in time (Rothman, Greenland, & Lash, 2008), as:

$$\mathbf{P_1} = \frac{(\mathbf{I_1}/100)\times\mathbf{D}}{1+(\mathbf{I_1}/100)\times\mathbf{D}} + P_0 \text{ (eq. 3)}$$

In this formula, the first term reflects ARB carriage that stems from food, water or livestock contacts, while the second term, P_0, reflects ARB carriage that stems from other sources. This prevalence P_1 may be used as an input in sub-models H1 and H2 that compute the incidence of acquisition of the ARB due to contacts with humans within hospitals and the community, assuming the prevalence upon hospital admission equal to the global community prevalence.

(d) The final incidence **I** (per 100 individuals, per year) may then be computed as a sum of these two functions of P_1:

$$\mathbf{I} = \mathbf{I_{H1}}(\mathbf{P_1}) + \mathbf{I_{H2}}(\mathbf{P_1}) \qquad \text{(eq. 4)}$$

Finally, this 1-year incidence can be transformed into a probability **R** of acquisition (risk) of the ARB over 1 year ranging from 0 to 1, by truncating at 1 the incidence **I** as follows:

$$\mathbf{R} = \min(\mathbf{I};1) \qquad \text{(eq. 5)}$$

Because many of the processes associated with resistance selection and dissemination are unknown, and the model developed here did not aim at reproducing mechanisms with precision, we used simple functions to model associations between variables. We assumed that a single exposure to the ARB was sufficient to initiate colonization and that the survival of the microorganisms was independent of any other microorganisms within the host. The risk associated with a repeated exposure was modelled using a binomial distribution. We assumed that the ARB amplification following at-risk exposure, such as antibiotic misuse or bad practices, was saturated, reaching a plateau for high levels of at-risk exposure. Hence, we systematically used the following function to model the amplification in ARB prevalence *X* due to a level *L* of at-risk exposure:

$$X \rightarrow X^{1/(1+L)} \qquad \text{(eq. 6)}$$

Conversely, we assumed that the impact in terms of ARB clearance of hygiene efforts or decontamination procedures was exponential, using the following function to model the decrease in ARB prevalence *X* due to a level *L* of hygiene or decontamination:

$$X \rightarrow X.e^{-L} \qquad \text{(eq. 7)}$$

2.2. Reservoirs sub-models

2.2.1 Water-related sub-model

The risk assessment model relating to water exposure covers all processes from water contamination to water consumption, and is illustrated in Fig. 2. The resulting incidence of

ARB acquisition over a year per 100 individuals $\mathbf{I_W}$ is computed from the number of days of tap water consumption per year *W_dose* and the probability of contamination via drinking water P_{colW}, using a binomial distribution as follows:

$$\mathbf{I_W} = \text{Bin}(W_dose*100, P_{colW}) \quad \text{(eq. 8)}$$

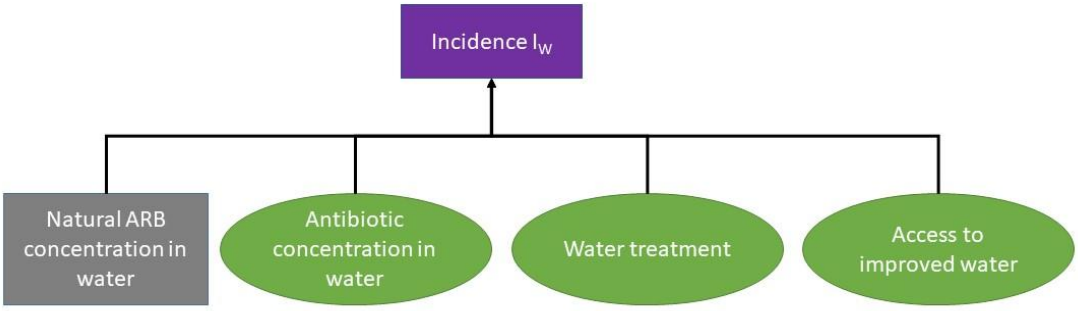


Fig. 2. Model of ARB acquisition via water consumption. Ellipses represent ARB drivers that may be impacted by interventions, while grey rectangles represent other ARB drivers that are held constant in this study.

The probability of ARB acquisition by an individual through drinking water P_{colW} is computed as the product of ARB concentration in natural water *W_sel*, multiplied by a corrective factor to account for the quality of the consumed water, *W_conso*, and the risk of ARB acquisition following ingestion of contaminated water *W_acq*:

$$P_{colW} = W_sel \times W_conso \times W_acq \quad \text{(eq. 9)}$$

- **ARB concentration in natural water**

We assume a baseline level of ARB presence in water *W_pres*, resulting mostly from community, hospital or livestock waste (Fuentefria, Ferreira, & Corcao, 2011; Sapkota, Curriero, Gibson, & Schwab, 2007). Several studies have measured ARB concentration in natural water in the South or Southeast Asia (SSA) region (Rashid, Rakib, & Hasan, 2015; Sapkota et al., 2007; Talukdar et al., 2013). ARB concentration in water can be amplified by the presence of antibiotics *W_atb* (Baquero, Martinez, & Canton, 2008). In SSA, antibiotics are mostly released by hospitals, pharmaceutical industries or livestock, and studies showed that concentration of antibiotics in water remained high even after wastewater treatment (Akiba et al., 2015; Diwan et al., 2010; Larsson et al., 2014; Lin, Lai, Tung, & Lin, 2015; Mutiyar & Mittal, 2014; Sim et al., 2011). Hence, *W_sel* is computed as:

$$W_sel = W_pres^{(1/(1 + W_atb))} \quad \text{(eq. 10)}$$

- **Impact of water treatment and access to safely managed water:**

Treatment and disinfection of drinking water may reduce the level of ARB contamination in water. Little information is available about quality of treatment in SSA . Access to improved water is highly variable across SSA : in Nepal, only 27% of population have access to improved water on premises, compared to 94% in Korea (WHO & UNICEF, 2014, 2017). The impact of water treatment on contamination of drinking water is computed from the treatment efficacy *W_treat* and the probability of access to treated water *W_access*:

$$W_conso = W_access \times e^{-W_treat} + (1 - W_access) \quad \text{(eq. 11)}$$

The variables included in the water sub-model are summarized in Table I.

Table I. Characteristics of parameters used for the water-related sub-model

Variable	Definition	Possible values
W_pres	Natural ARB concentration in water	Continuous variable in [0,1]
W_atb	Presence of antibiotics in water	0: none / 1: low / 2: average / 3:high
W_treat	Management of drinking water	0: neutral / 0.5: reduces ARB by 40% / 1: reduces ARB by ~60% / 2: reduces by 85% / 3: reduces by 95%
W_access	Percentage of the population with access of improved water on premises	Continuous variable in [0,1]
W_acq	Probability of acquisition of ARB following ingestion of contaminated water on a day	Continuous variable in [0, 1]
W_dose	Number of days of tap water consumption over a year	Integer in $[\![0,365]\!]$

2.2.2 Food-related sub-model

The food-processing step is an important component where ARB can be selected or controlled. This includes food transportation, food storage, and retail on markets. The last component is the consumer who will store, prepare, cook, and consume the food. Here, we focused on ARB acquisition through meat consumption, as recent data suggests that meat is the main source of AMR exposure among food products (Jans et al., 2018). The risk assessment model due to food exposure covers all processes from animal production to meat consumption and is illustrated in **Fig. 3**. The resulting incidence of ARB acquisition by food consumption over a year per 100 individuals $\mathbf{I_F}$ is computed from the number of days of meat exposure *F_dose* per year, and the probability of colonisation via food P_{colF}, as follows:

$$\mathbf{I_F} = Bin(F_dose*100\ ,\ P_{colF}) \quad \text{(eq. 12)}$$

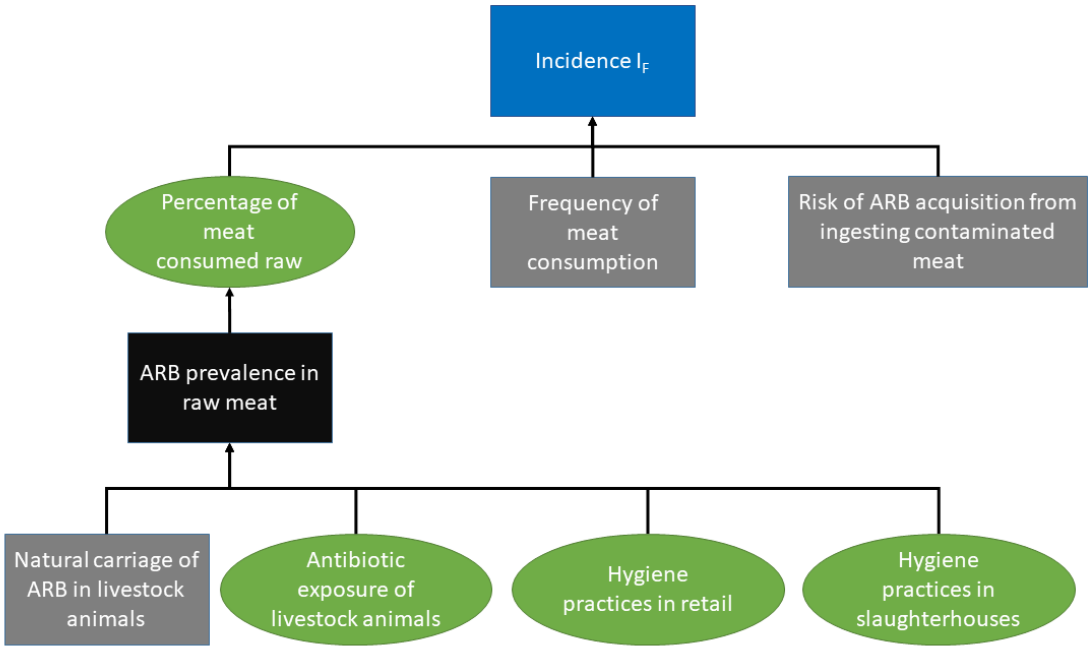


Fig. 3. Model of ARB acquisition via food consumption. Ellipses represent ARB drivers that may be impacted by interventions, while grey rectangles represent other ARB drivers that are held constant in this study.

The probability of colonisation via consumed meat P_{colF} is computed as the product of ARB prevalence in animals coming from farms *F_arb* amplified by inappropriate slaughter and retail treatment of the meat *F_treat*, the effect of food preparation on ARB contamination *F_cook*, and the risk of ARB acquisition following the ingestion of contaminated food *F_acq*:

$$P_{colF} = F_arb^{F_treat} \times F_cook \times F_acq \quad \text{(eq. 13)}$$

- **Antibiotic selection model in meat-producing animals:**

Antibiotic exposure in farms exerts a selective pressure, which amplifies ARB prevalence in meat-producing animals. Antibiotics are largely used in SSA farms for prophylaxis and metaphylaxis (Archawakulathep et al., 2014; Laxminarayan & Chaudhury, 2016; Thomas P. Van Boeckel et al., 2017). Here, we assume a baseline level of presence of the bacteria in animals and meat when antibiotics are not used, *F_prev*. This prevalence is amplified according to antibiotic use for production in farms *F_atb*:

$$F_arb = F_prev^{(1/(1+F_atb))} \quad \text{(eq. 14)}$$

- **Impact of inappropriate slaughter and retail treatment**

Hygiene and disinfection levels at slaughter and during retail may also reduce or amplify the level of ARB contamination in products. In most countries of the region, there is no food safety policy or weak program implementation (WHO/SEARO, 2014). Poor hygiene practices during slaughter were also reported, potentially leading to meat contamination (Boonyasiri et al., 2014; Chotinun, Rojanasthien, Unger, Tadee, & Patchanee, 2014), and poor food safety during subsequent meat handling. Here, the levels of hygiene and disinfection at slaughter, *F_slaugh*, and during retail, *F_ret*, may either be negative (modelling good hygiene or disinfection procedures leading to ARB reduction) or positive (modelling low hygiene and disinfection, leading to amplification of the level of ARB in product).
The effect of slaughter and retail treatment *F_treat* is modelled as follows:

$$F_treat = 1 / ((1+F_slaugh) (1+F_ret)) \quad \text{(eq. 15)}$$

- **Impact of cooking on ARB elimination / inactivation**

While cooking has been shown to efficiently eradicate bacteria (Boonyasiri et al., 2014), consumption of raw meat and insufficient cooking are important risk factors of acquisition. In Thailand, Nham (a very popular sausage) is made from raw meat, left to ferment at ambient temperature for up to 4 days and usually consumed without cooking. Such recipes are typical sources of undesirable microorganisms such as *Salmonella spp*., *S. aureus*, and *Listeria monocytogenes* (Swetwiwathana & Visessanguan, 2015). We assume that cooking reduces strongly the rate of ARB by killing the bacteria. When the product is consumed raw, food preparation does not impact ARB contamination. The effect of food preparation on ARB, *F_cook*, is thus modelled through an empirical function of the percentage of raw food consumption *F_raw:*

$$F_cook = \begin{cases} 1 \text{ with probability } F_raw \\ 0.01 \text{ with probability } (1-F_raw) \end{cases}$$

The variables included in the food submodel are summarized in Table II.

Table II. Characteristics of parameters used for the food-related sub-model

Variable	Definition	Possible values
F_prev	Prevalence of natural ARB in animals	Continuous variable in [0,1]
F_atb	Level of antibiotic use for production in farms	0: no use / 1: low / 2: average / 3:high
F_slaugh	Level of hygiene at slaughter	Continuous variable in]-1, 1[<0: eliminates ARB / 0: neutral / >0: expends ARB
F_ret	Level of hygiene / temperature and general conditions in retail	Continuous variable in]-1, 1[<0: eliminates ARB / 0: neutral / >0: expends ARB
F_raw	Percentage of raw food consumption	Continuous variable in [0, 1]
F_dose	Frequency of meat consumption in the population over a year	Integer in $[\![0,365]\!]$
F_acq	Probability of acquisition of bacteria when consuming contaminated product	Continuous variable in [0,1]

2.2.3 Livestock contact-related sub-model

In most countries of SSA , livestock are mainly raised in small-sized family-type farms, with a large proportion of the rural population possessing one or several livestock species. For instance, in India, based on a 2012 survey (India Human Development Survey-II, 2011-12),

42% of households own livestock animals, with most livestock producers operating on a small scale. Similarly, in Thailand, nearly 50% of pig holdings include less than 2 pigs and less than 2% include more than 50 pigs (FAO). However, commercial (or industrial) farming is currently expanding, with a potentially important impact on ARB spread, as practices differ widely between family-type and industrial-type farms. The risk assessment model due to livestock contacts characterizes all human contacts with livestock animals occurring within both types of farms and is illustrated in Fig. 4. The resulting incidence of ARB acquisition over a year per 100 individuals $\mathbf{I_L}$ is computed from the probability of being involved in husbandry *L_husb*, the proportion of family-type farms in the country *L_PHFam*, the mean number of contacts per person with livestock animals over 1 year *L_NCtc*, and the per-contact acquisition risk *RCtc*, according to the type of farms (denoted by the subscript F for family, I for industrial), as follows:

$$\mathbf{I_L} = L_husb \times [L_PHFam \times Bin(L_NCtc_F * 100, RCtc_F) + (1 - LPHFam) \times Bin(L_NCtc_I * 100, RCtc_I)] \quad \text{(eq. 16)}$$

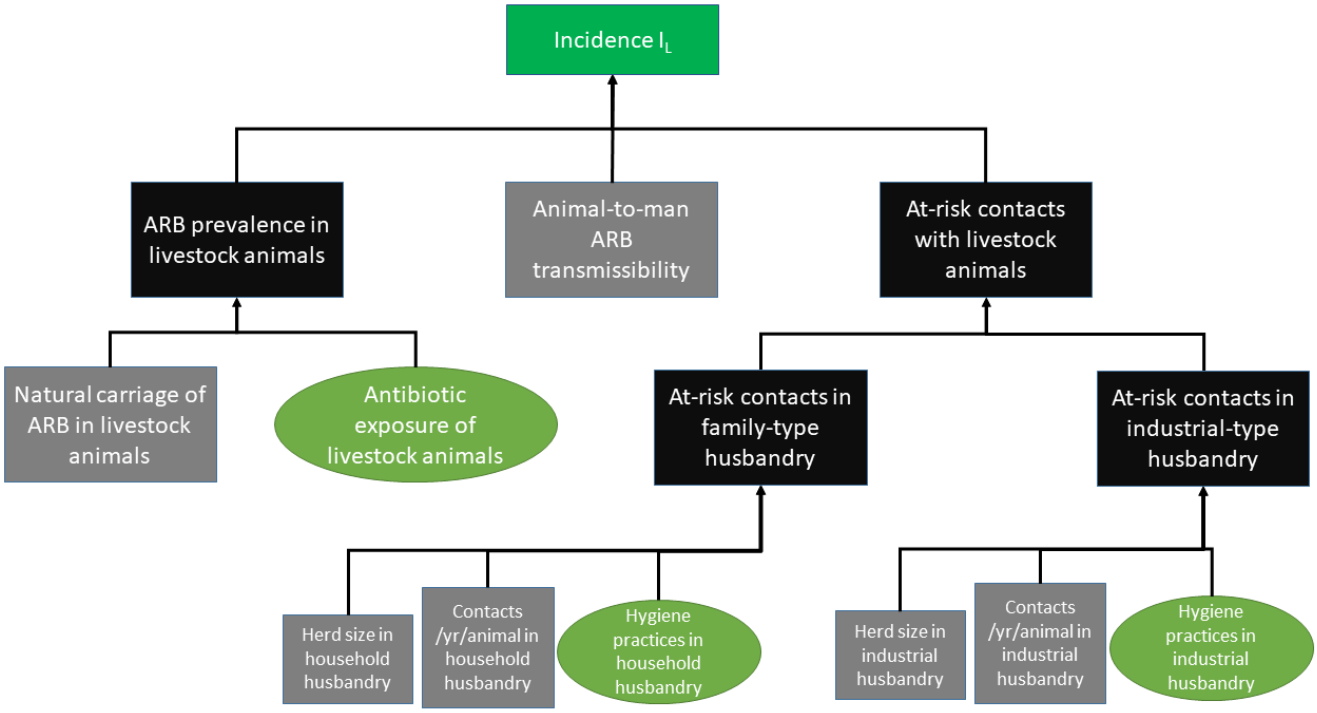


Fig. 4. Model of acquisition via livestock contacts. Ellipses represent ARB drivers that may be impacted by interventions, while grey rectangles represent other ARB drivers that are held constant in this study.

- **Number of contacts with animals**

The total number of contacts with animals per year in each type of farm for a given individual being involved in husbandry results from the yearly frequency of human-animal contacts in this farm type (L_CtcAH_F or L_CtcAH_I, respectively in family-type and industrial-type farms), and from the average number of animals in this farm type (L_Na_F or L_Na_I, respectively in family-type and industrial-type farms):

$$L_NCtc_F = L_Na_F \times L_CtcAH_F \quad \text{(eq. 17)}$$

$$L_NCtc_I = L_Na_I \times L_CtcAH_I \quad \text{(eq. 17)}$$

- **Per contact acquisition risk**

For a human to acquire ARB after a contact with livestock, there either needs to be transmission of a pathogenic resistant bacterium from animal to human, or transmission of a non-pathogenic resistant bacterium followed by within-host transfer of genetic material to a pathogenic bacterium. As a first approximation, we will neglect this second possibility and focus on the first situation (direct transmission of a resistant bacterium). The risk of this transmission during a contact depends on the probability L_*pBMR* that the animal is colonized by a resistant bacterium, on the animal-man transmissibility *L_tAH* of this bacterium, and on hygiene and control measures taken during the contacts *L_Hyg*. Both L_*pBMR* and *L_Hyg* may depend on the farm type, denoted as the subscript F for family-type farms or I for industrial-type farms:

$$RCtc_F = L_pBMR_F \times L_tAH \times e^{-L_HygF} \quad \text{(eq. 18)}$$

$$RCtc_I = L_pBMR_I \times L_tAH \times e^{-L_HygI} \quad \text{(eq. 18)}$$

The probability L_*pBMR* that a livestock animal carries a resistant bacterium results from the "natural" prevalence *L_prev* of ARB in livestock animals, over which little data is available, and from antibiotic exposure *L_atb* of livestock animals. The latter depends on the farm type (denoted again as F or I) and has been reported to be very high in countries such as India or Indonesia, with antibiotics used as growth promoters, especially in industrial-type settings (Brower et al., 2017; Thomas P Van Boeckel et al., 2015), leading to ARB selection:

$$L_pBMR_F = L_prev^{(1/(1+ L_atbF))} \quad \text{(eq. 19)}$$

$$L_pBMR_I = L_prev^{(1/(1 + L_atbI))} \quad \text{(eq. 20)}$$

The variables included in the livestock contact model are summarized in Table III.

Table III. Characteristics of parameters used for the livestock contact-related sub-model

Variable	Definition	Possible values
L_husb	Portion of individuals involved in husbandry	Continuous variable in [0,1]
L_tAH	Probability of human ARB acquisition during a contact with a colonized animal	Continuous variable in [0,1]
L_prev	Probability of animal colonization	Continuous variable in [0,1]
L_PHFam	Portion of family-type farms (as opposed to industrial-type farms)	Continuous variable in [0,1]
L_Na_F / L_Na_I	Average number of animals per family-type or industrial-type farm	Integer in $[\![0,200]\!]$
L_CtcAH_F / L_CtcAH_I	Number of animal-human contacts, per animal and per year, for family-type or industrial-type farms	Integer in $[\![0,365]\!]$
L_atb_F / L_atb_I	Level of animal exposure to antibiotics in family-type or industrial-type farms	0: none/ 1: low/ 2: medium/ 3: high

L_Hyg$_F$ / L_Hyg$_I$	Probability of compliance to hygiene and control measures during human-animal contacts, in family-type or industrial-type farms	Continuous variable in [0,1]

2.2.4 Hospital-related sub-model

The risk assessment model due to hospital contamination is based on a characterization of at-risk contacts within hospitals, and is illustrated in Fig. 5. The resulting incidence of ARB acquisition over a year per 100 individuals $\mathbf{I_{H1}}$ is computed from the number of hospitalization days over 1 year per person, *H_Nhospit*, and the acquisition risk over a single day of hospitalization probability P_{colH}, as follows:

$$\mathbf{I_{H1}} = Bin(H_Nhospit * 100, P_{colH}) \qquad \text{(eq. 21)}$$

The risk of acquiring an ARB over 1 day of hospitalization P_{colH} is computed as the product of ARB prevalence at hospital admission *H_Padm*, amplified by antibiotic exposure within the hospital *H_atb*; the level of inter-individual transmission within the hospital *H_trans*, amplified by the frequency of multiple rooms (that is, rooms hosting multiple patients) within the hospital *H_Fmr*; and another amplifying factor related to level of hygiene within the hospital *H_hyg*:

$$PcolH = H_Padm^{(1/(1+ H_atb))} \times H_trans^{(1/(1+H_Fmr))} \times e^{-H_hyg} \qquad \text{(eq. 22)}$$

As explained earlier, the prevalence at hospital admission *H_Padm* may be computed from the outputs of the first three submodels and a term P_0 reflecting other ARB sources.

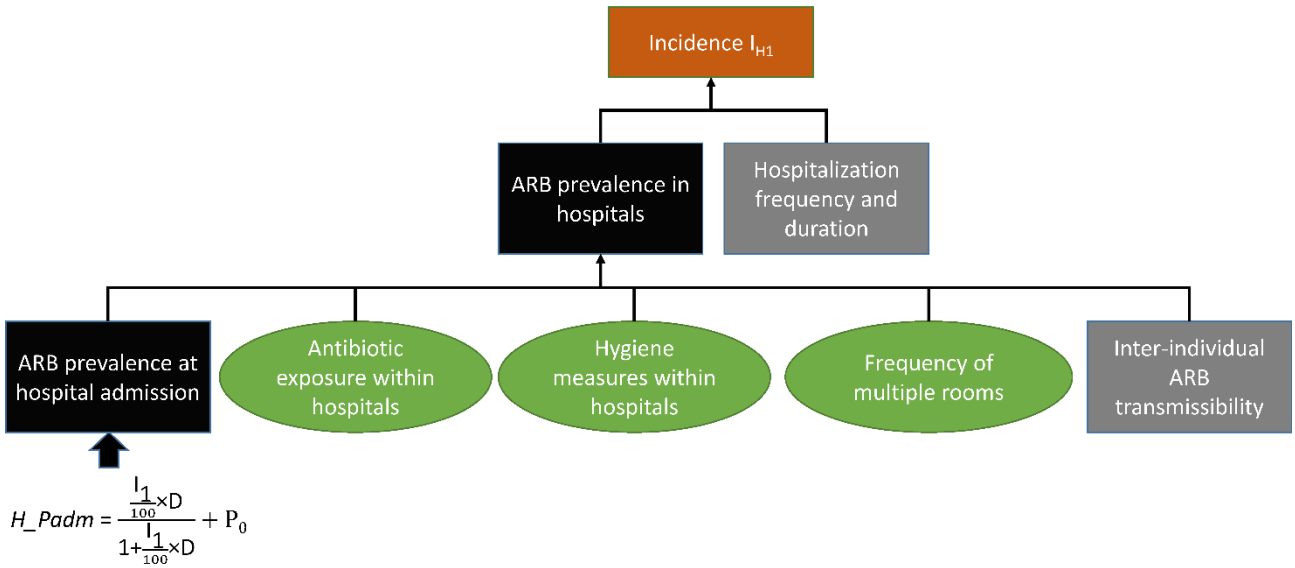


Fig. 5. Model of acquisition via hospital. Ellipses represent ARB drivers that may be impacted by interventions, while grey rectangles represent other ARB drivers that are held constant in this study. ARB prevalence at hospital admission is computed from the incidence I_1 based on equation 3.

The variables included in the hospital submodel are summarized in Table IV.

Table IV. Characteristics of parameters used for the hospital-related sub-model

Variable	Definition	Possible values

H_Nhospit	Number of hospital days per year, per person	Integer in $[\![0,365]\!]$
H_Padm	Probability of ARB carriage at hospital admission	Continuous variable in [0,1]
H_atb	Level of patient antibiotic exposure within hospitals	0: none/ 1: low/ 2: medium/ 3: high
H_trans	Probability of patient ARB acquisition during a contact with a colonized patient within a hospital	Continuous variable in [0,1]
H_Fmr	Level of frequency of multiple rooms within hospitals	0: none/ 1: low/ 2: medium/ 3: high
H_hyg	Probability of compliance to hygiene and other infection control measures within hospitals	Continuous variable in [0,1]

2.2.5 Community transmission model

The risk of transmission in the community can be modulated by two principal factors: antibiotic misuse and hygiene. The resulting incidence of ARB acquisition over a year per 100 individuals I_{H2} is computed from the number of days of exposure to other individuals *C_dose* and the probability of acquisition when exposed to them P_{colC}, as follows:

$$I_{H2} = Bin(100*C_dose, P_{colC}) \quad \text{(eq. 23)}$$

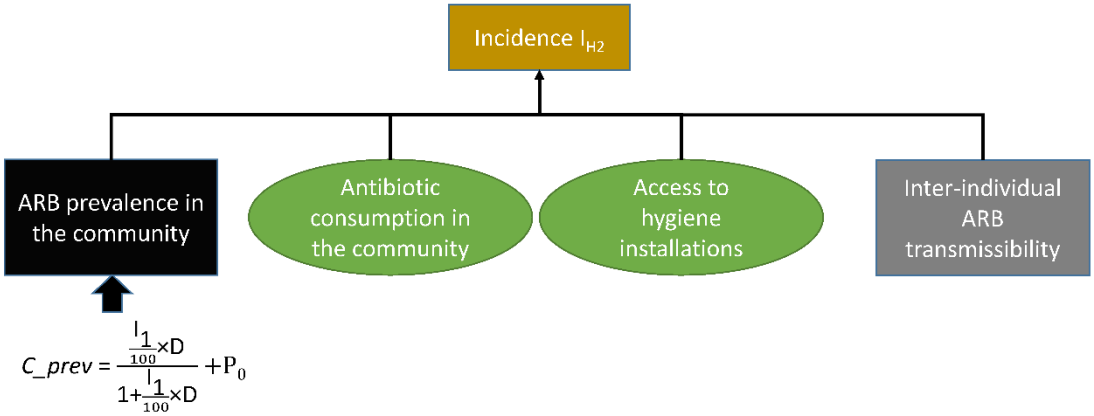


Fig. 6. Model of acquisition via the community. Ellipses represent ARB drivers that may be impacted by interventions, while grey rectangles represent other ARB drivers that are held constant in this study. ARB prevalence in the community is computed from the incidence I_1 based on equation 3.

For a given individual, the risk of acquisition over a day P_{colC} is computed as the product of the prevalence of ARB in community *C_sel* and transmission risk during contacts with colonised *C_trans*, impacted by the effects of not having access to basic hygiene installations *C_effhyg* and to private sanitation *C_effpsan*:

$$P_{colC} = C_sel \times C_trans^{\,1/(1 + C_effhyg \times C_effsan)} \quad \text{(eq. 24)}$$

- **Antibiotic selection in the community:**

Antibiotic consumption by individuals in the community exert a selective pressure that amplifies prevalence. In some countries of SSA , antibiotic consumption is very high

(Kathleen Anne Holloway, 2011; WHO, 2015). In 2009, a study evaluated that more than one billion units of antibiotics were sold in India (Ganguly et al., 2011). In 2014, antibiotics were accessible without prescription in more than half of SSA countries and most of the countries reported that quality could be enforced (K. A. Holloway, Kotwani, Batmanabane, Puri, & Tisocki, 2017). In almost all countries, necessary public information campaigns on antimicrobial use are ongoing or have already been conducted: a lack of knowledge was observed in physicians and community (WHO, 2015, 2017; WHO/SEARO, 2011). Misuse can fluctuate according to countries, regulation policies, and public awareness. Here, we assume a baseline level of presence of the bacteria in the community when antibiotics are not used *C_prev*. It is amplified by the misuse of antibiotics *C_atb*. The resulting prevalence, *C_sel*, is modelled as follows:

$$C_sel = C_prev^{(1/(1+C_atb))} \qquad \text{(eq. 25)}$$

As explained earlier, the baseline prevalence in the community *C_prev* may be computed from the outputs of the first three submodels and a term P_0 reflecting other ARB sources.

- **Impact of hygiene**

Two hygiene factors may affect ARB transmission in the community: hygiene practices, such as hand hygiene, and access to private (individual) sanitation. Access to private sanitation and hygiene services differ by country. In 2015, the percentage of population with access to basic hygiene facilities (handwashing facility with soap and water available on premises) varied from 87% in Bhutan to 40% in Bangladesh (WHO & UNICEF, 2017). Shared sanitary were used by 2% of population in Sri Lanka and Maldives versus 22% in Bangladesh (WHO & UNICEF, 2017). We assume that poor access to proper sanitation and hygiene services increases the transmission risk.

$$C_effpsan = \begin{cases} 0 \text{ with proba } (C_psan) \\ 1 \text{ with proba } (1-C_psan) \end{cases}$$

$$C_effhyg = \begin{cases} 0 \text{ with proba } (C_hyg) \\ 1 \text{ with proba } (1-C_hyg) \end{cases}$$

The variables included in the community submodel are summarized in Table V.

Table V. Characteristics of parameters used for the community-related sub-model

Variable	Definition	Possible values
C_prev	ARB prevalence in the community	Continuous variable in [0,1]
C_atb	Frequency of antibiotics misuse in the community	Continuous variable in [0,1]
C_hyg	Percentage of population with access to hygiene installation	Continuous variable in [0,1]
C_psan	Percentage of population with access to private sanitation	Continuous variable in [0,1]
C_trans	Transmission risk during contacts with colonised	Continuous variable in [0, 1]

C_dose	Frequency of exposure to other individuals over a year	Integer in $[\![0,365]\!]$

2.3. Application to two illustrative contexts

The default mean values for parameters were set based on a non-exhaustive literature review of extended spectrum beta-lactamase producing *Enterobacteriaceae* (ESBL-PE) prevalence, antibiotic use, and context in SSA. First, the baseline simulation of the risk was assessed over the range of values for all parameters. The model was then applied in two distinct scenarios. Scenario A illustrates the situation in a south-Asian developing country with poor sanitation and infrastructures (e.g. Nepal); whereas scenario B illustrates the situation in a high-income Asian country (e.g. Singapore, South-Korea). For simplicity reasons, only a single parameter per sub-model was allowed to vary between these two sets. Table 6 provides the full list of model parameters with their assumed baseline values, as well as values for scenarios A and B. In this application, the term P_0 reflecting potential sources of ARB within human populations beyond food, water or livestock contacts was assumed null.

Table VI. List of model parameters with their values in the baseline, A (lower-middle-income Asian country) and B (higher-middle-income Asian country) scenarios. Parameter values are assumed to follow either uniform distributions (in which case the distribution is provided as Uniform(min,max)) or Gaussian distributions (in which case the distribution is provided as Normal(mean,standard deviation)).

Parameter	Variable	Baseline	Scenario A (lower-income country)	Scenario B (higher-income country)	References
Water model					
Natural ARB concentration in water	*W_pres*	Uniform(0.29,0.6)			(Baquero et al., 2008; Rashid et al., 2015; Sapkota et al., 2007; Talukdar et al., 2013)
Presence of antibiotics in water	*W_atb*	Uniform(0,1)			(Baquero et al., 2008; Diwan et al., 2010; Larsson et al., 2014; Lin et al., 2015; Mutiyar & Mittal, 2014; Sim et al., 2011)
Management of drinking water	*W_treat*	Uniform(1,2)			(Baquero et al., 2008)
Percentage of the population with access of improved water on premises	*W_access*	Uniform(0.3,0.8)	Uniform(0.3; 0.4)	Uniform(0.7;0.8)	(WHO & UNICEF, 2014, 2017)

Probability of acquisition of ARB following ingestion of contaminated water on a day	*W_acq*	Normal(0.05,0.01)			Assumed
Frequency of water consumption over a year	*W_dose*	Normal(mean=360)			Assumed
Food model					
Prevalence of natural ARB in animals	*F_prev*	Uniform(0.01,0.15)			(Boonyasiri et al., 2014)
Level of antibiotic use for production in farms	*F_atb*	Uniform(2,3)			(Archawakulathep et al., 2014; Laxminarayan & Chaudhury, 2016; Thomas P Van Boeckel et al., 2014)
Level of bad hygiene in practice at slaughter	*F_slaugh*	Normal(0,0.1)			(Boonyasiri et al., 2014; Chotinun et al., 2014; Kluytmans et al., 2013)
Level of hygiene / temperature and general conditions in retail	*F_ret*	Uniform(-0,5,0,5)	Uniform(0.1;0.5)	Uniform(-0.5;-0.1)	(Boonyasiri et al., 2014)

Percentage of raw food consumption		*F_raw*	Normal(0.2,0.01)			(Van De, Le, Lien, & Eom, 2014)
Frequency of meat consumption in the population over a year		*F_dose*	Normal(50,10)			(Nam, Jo, & Lee, 2010)
Probability of acquisition of bacteria when consuming contaminated product		*F_acq*	Normal(0.1,0.01)			Assumed
Livestock model						
Percentage of individuals involved in husbandry		*L_husb*	Normal(0.7, 0.1)	Normal(0.8, 0.1)	Normal(0.3, 0.1)	(Brower et al., 2017; Desai & Vanneman, 2015; FAO)
Baseline risk of transmission during human-animal contacts		*L_tAH*	Uniform(0.001, 0.005)			Assumed
Prevalence in animals / carriage probability		*L_prev*	Uniform(0.01; 0.05)			(Boonyasiri et al., 2014; Brower et al., 2017)
Proportion of husbandry in family context, i.e. small (the other part being industrial farms, i.e. big farms)		*L_PHFam*	Uniform(0.35,0.95)			(Brower et al., 2017; Desai & Vanneman, 2015; FAO)
Number of animals per farm	*Family farms*	L_Na_F	Normal(10, 2)			(Desai & Vanneman, 2015;
	Industrial farms	L_Na_I	N(200, 20)			

				FAO)
Number of human-animal contacts, per animal and per year	*Family farms*	L_CtcAH_F	365 contacts per year	(Desai & Vanneman, 2015; FAO)
	Industrial farms	L_CtcAH_I	52 contacts per year (1/week/animal)	
Level of proportion of animals exposed to antibiotics	*Family farms*	L_atb_F	Uniform(1,2)	(Thomas P Van Boeckel et al., 2015)
	Industrial farms	L_atb_I	Uniform(2,3)	
Level of hygiene and control measures during contacts, equivalent to % of individual compliance	*Family farms*	L_Hyg_F	Uniform(0.1,0.3)	Assumed
	Industrial farms	L_Hyg_I	Uniform(0.4,0.6)	
Hospital model				
Number of hospital days per year, per person		*H_Nhospit*	Normal(0.45,0.05)	(Chompook, Sa, Hanvoravongchai, Lertiendumrong, & Putthasri, 2009; Mahendradhata et al., 2017)
Carriage prevalence at admission		*H_Padm*	Normal(0.3,0.05)	(Azim et al., 2010; Thuy et al., 2017)

Percentage of hospital patients exposed to antibiotics	*H_atb*	Uniform(1,2)			(Gandra et al., 2017)
Baseline risk of transmission during patient contacts within hospitals	*H_trans*	Normal(0.2; 0.01)			Assumed
Frequency of multiple rooms within hospitals	*H_Fmr*	Uniform(1,2)			Assumed
Level of hygiene and control measures during contacts, equivalent to percentage of compliance	*H_hyg*	Uniform(0.2,0.4)	Uniform(0.2,0.3)	Uniform(0.5,0.6)	(Santosaningsih et al., 2017; Sastry, R, & Bhat, 2017)
Community model					
Prevalence in the community	*C_prev*	Normal(0.3,0.05)			
Frequency of antibiotics misuse in the community	*C_atb*	Uniform(0.15,0.55)	Uniform(0.4,0.55)	Uniform(0.15,0.30)	(Ganguly et al., 2011; K. Holloway, Mathai, & Gray, 2011; K. A. Holloway et al., 2017; WHO, 2015; WHO/SEARO, 2011)
Percentage of population with access to hygiene installations	*C_hyg*	Mean = 0.6			(WHO & UNICEF, 2014, 2017)
Percentage of population with access to private sanitation	*C_psan*	Mean = 0.9			(WHO & UNICEF, 2014, 2017)

Transmission risk during contacts with colonised individuals	*C_trans*	Normal(0.01, 0.001)	Assumed
Frequency of exposure to other individuals over a year	*C_dose*	360	Assumed

2.4. Implementation

The hierarchical model was built using the R platform (www.r-project.org) and mc2d package (Pouillot & Delignette-Muller, 2010). At the first level, each source-associated incidence was computed. At the second level, these incidences were combined to assess the global acquisition risk for humans. Two-dimensional Monte Carlo simulations were run to compute these incidences for each component and the global risk. All distributions for parameters represent a combination of the parameters' uncertainty (due to limited or imperfect knowledge) and variability. For each simulated scenario, 100,000 iterations were run.

3. RESULTS

3.1. Predicted incidence and risk of AMR acquisition

The predicted distribution of the yearly incidence rates for each sub-model is provided in Fig. 7. Scenario B (high level of development setting, Fig. 7B) led to much lower overall incidences of acquisition of the ARB from contacts with livestock than scenario A (low level of development setting, Fig. 7A) and the baseline scenario (Fig. 7C) with median (95%Confidence interval [CI]) incidences of 98 [22,286], 275 [84,667], and 241 [72,589] acquisitions of the ARB per 100 individuals and per year respectively. The same was true for incidences of ARB acquisition due to consumption of contaminated water (425 [215,724], 740 [386,1182], 572 [266,1050] respectively). When adding in the transmission process from the hospital and community, the three scenarios also predicted distinct average risks, 67% [18%,100%], 100% [66%,100%], and 100% [41%,100%] respectively, of acquiring at least once a resistant bacteria over a year.

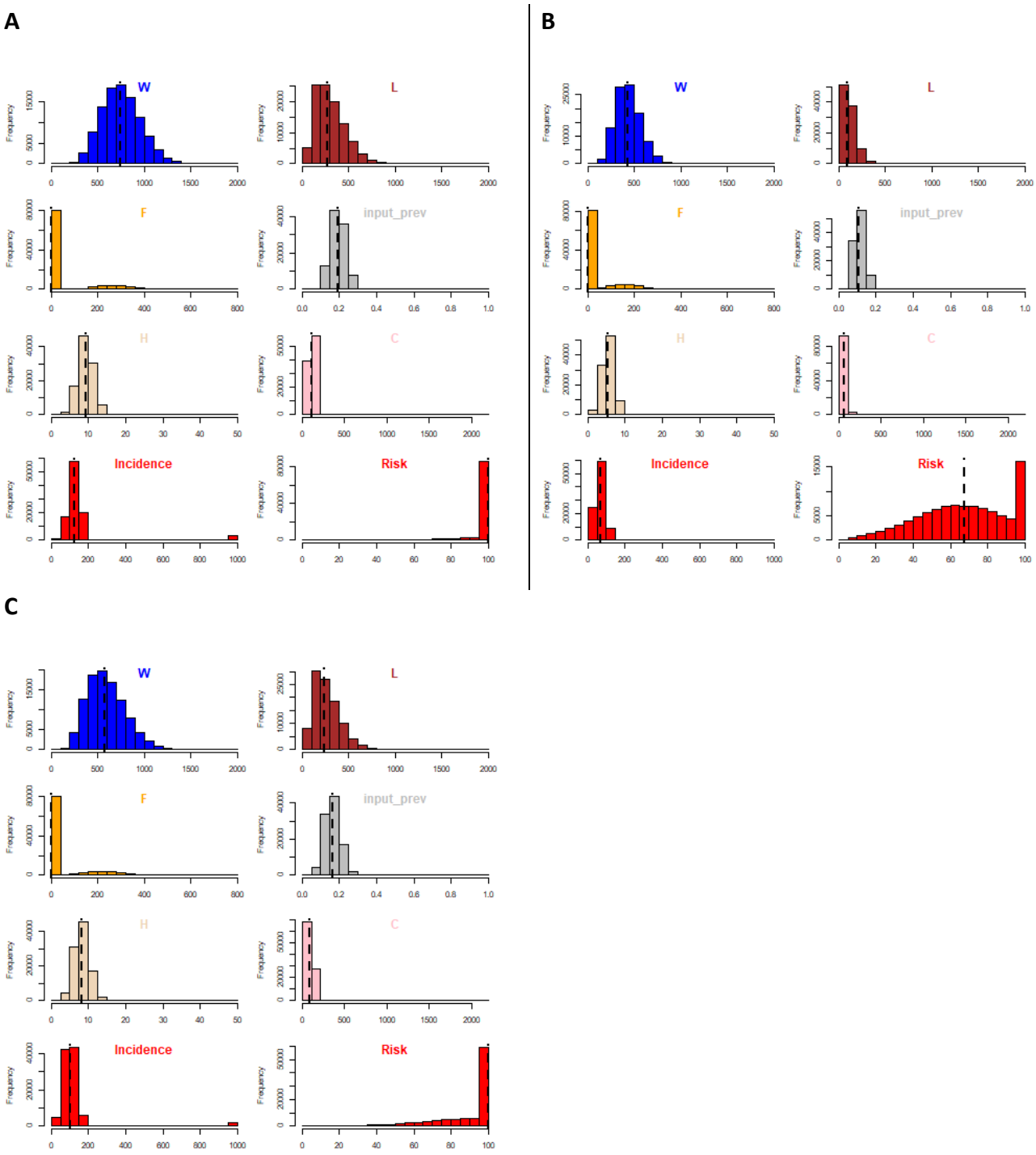


Fig. 7. Model-predicted distributions for three scenarios. The figure shows the distributions of the predicted yearly incidences of ARB acquisition for 100 human individuals from the different reservoirs in (A) scenario A (low level of development setting), (B) scenario B (high level of development setting), and (C) the baseline scenario. W: water (blue); L: livestock (brown); F: food (orange); H: hospital (beige); and C: community (pink). Input_prev (in grey) represents the predicted prevalence in humans resulting from acquisition from the W, L, and F reservoirs. It is an input parameter of the H and C models. "Incidence" and "Risk" (in red) represent respectively the distributions of the acquisition incidence over a year (saturated at 1000 for illustration purposes) and yearly acquisition risk per 100 individuals. The black dashed lines indicate the median value of each predicted distribution.

3.2. Sensitivity analysis

We performed a sensitivity analysis exploring the five parameters varied across scenarios A, B and baseline (Fig. 8). The parameters that had the highest impact on the final incidence of resistant bacteria acquisition in the population were the percentage of population with access to improved water on premises and the percentage of individuals in the population involved in husbandry. Interestingly, the model did not show a strong impact of the level of conditions in retail nor level of hygiene in hospitals.

In order to assess the impact of the different parameters on the predicted incidence of ARB acquisition at each level, we also carried out multivariate sensitivity analyses. Fig. S1 shows for each submodel the Spearman rank correlation of all model parameters with the resulting incidence of ARB acquisition related to this submodel, together with their 95% confidence intervals. Parameters with the highest Spearman rank correlation were the percentage of population with access to improved water and premises (*W_access, r*= -0.57 [-0.61; -0.52*]*) for the water submodel, the percentage of raw food consumption (*F_raw* and *F_cook*=0.68 []0.65;0.72) for the food submodel, the probability of human ARB acquisition during a contact with a colonized individual (*L_taH*=0.77 [0.75;0.8]) for the livestock submodel, the number of hospital days per year, per person (*H_Nhospit*, r=0.44 [0.38; 0.50]) for the hospital submodel and the frequency of antibiotic misuse in the community (*C_atb*, r=0.31 [0.24;0.37]) for the community submodel.

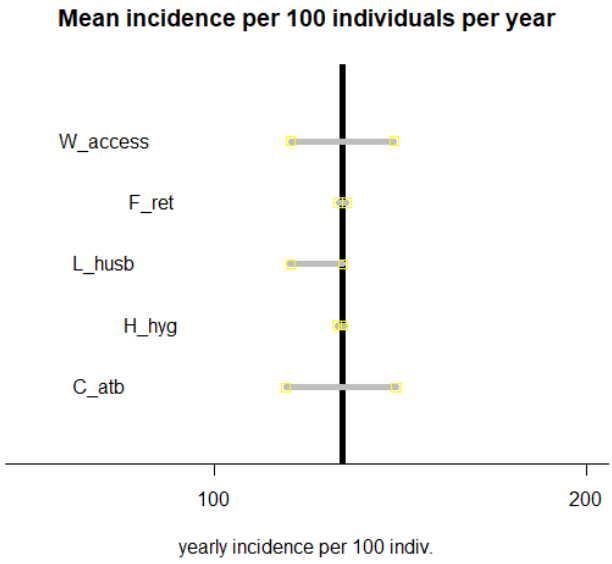


Fig. 8. Range of estimated incidence for selected parameters. The figure represents the average risk calculated over 100,000 repetitions of the model for the baseline scenario (black vertical line) and for extreme values of five parameters. W_access sampled in a Uniform distribution ranging respectively (0.3,0.4) and (0.7,0.8); F_ret sampled in a uniform distribution ranging respectively (0.1, 0.5) and (-0.5, -0.1); L_husb sampled in a Normal distribution of means 0.8 and 0.3 and standard deviation 0.1; H_hyg sampled in a Uniform distribution ranging (0.2,0.3) and (0.5,0.6) ; and C_atb sampled in a Uniform distribution ranging (0.4, 0.55) and (0.15,0.30).

4. DISCUSSION

We developed a risk assessment tool to assess the routes of acquisition of ARB in the south- or southeast-Asian context. This tool comes as a complement to already developed conceptual approaches for situational analysis in Asia (Chereau et al., 2017; WHO, 2019) and may prove useful for three main reasons.

First, as evidenced by our earlier work, there are many knowledge gaps that hinder our capacity to fully estimate the risk of ARB acquisition (Chereau et al., 2017). This is true in SSA but also anywhere in the world. In this regard, the illustrative scenarios provided here demonstrate that the tool we propose may be used to complement these identified gaps of knowledge and to assess the range of potential impacts that the related unknown or uncertain parameters may have on the risk of ARB acquisition in a given setting.

Second, we chose to apply the model to the specific case of ESBL-PE in two different typical countries for illustrative purposes. However, by adapting parameters values and/or deactivating some of the factors or submodels, the model could be applied to any other human bacterial species for which non-sexual human-to-human direct transmission exists and animal/environmental sources are known, e.g. *Salmonella spp*., *S. aureus*, any Enterobacteriaceae species, *Streptococcus pneumoniae* and *Listeria monocytogenes*. Importantly, we assumed P_0 as null in our application, but non-null values for this term may be used for ARB that arise directly in human populations or from sources other than food, livestock contacts or water. The model being generic, it could also be applied to countries from other parts of the world beyond SSA. Again, parameters and considered paths should be switched on and off to depict the most accurately possible the country-pathogen situation of interest.

Third, while its quantitative outputs should be taken with caution, this tool may also be used to provide qualitative predictions of the public health impact that could be expected following the implementation of control measures. In particular, it should allow ranking considered strategies according to their potential effectiveness. It may also help estimate the impact of governance, regulations, guidelines, and surveillance capacities on drivers at each key-step. To do so, it will be necessary to parameterize the model using realistic data from a specific country. The parameterized model will then be run to assess the impact on AMR of public health strategies such as decreasing antibiotic use in livestock, in the community or in hospitals; improving hygiene practices in husbandry, in hospitals or for food retail; etc.

4.1. Model validation

It should be underlined that, for many ARB, there is still a scarcity of data in SSA allowing full validation of model predictions, for instance on ARB prevalence in different subpopulations or antibiotic use in livestock animals throughout the region. However, using available data, it is possible to show that our model is able to provide consistent predictions.

For instance, in Thailand, a country which is thought to have a better food supply chain compared with other south-east Asian countries, ESBL-PE have been isolated in pork and chicken throughout the production chain, from farms (with 39% [28%-49%] of broilers and 69% [65%-74%] of pigs colonized), slaughterhouses (where 17% [0-34%] of pork meat samples were contaminated), up to markets retailers (with 36% [11%-61%] of contaminated chicken samples and 53% [28%-79%] of contaminated pork samples) (Boonyasiri et al., 2014). In the same study, ESBL-PE were also isolated in 60% [42%-78%] of humans working in contact with these healthy livestock animals. For this specific bacterium and setting, the model parameterization provides consistent predictions; for instance, for a baseline prevalence of ARB in meat-producing animals of 0.15, and an assumed high

level of antibiotic exposure in these animals, the formula we used yields a prevalence of 62% [min-max 0.61-0.63] of ARB in farm animals before slaughter; further assuming a high level of hygiene and disinfection at slaughter (*F_slaugh* = -0.7), and a moderately high level of bad retail practices (*F_ret* = 0.5), this yields a prevalence of ARB in meat after slaughter of 21% [min-max 0.21-0.26] and a prevalence of ARB in retailed meat of 35% [min-max 0.28-0.41]. Assuming mid-range animal-to-man ARB transmissibility and hygiene level on farms (*LtAH* = 0.004 and *Lhyg* = 0.3), this also yields a predicted prevalence of ARB carriage among humans working in a 100-animal livestock farm with daily contacts with livestock of 60% [min-max 0.46-0.68].

When focusing on a given SSA country for future model use, using similar prevalence data collected from surveys in water, in food, among livestock animals or their environment, and among humans would allow a fine calibration and/or validation of the model.

4.2. Model limitations

First, the main limitations of the proposed model relate to the assumptions we were forced to make due to the lack of available and accurate data. In many countries, precise estimates of model parameters are not available, as highlighted in our earlier work, making the model difficult to parameterize with precision (Chereau et al., 2017). This is for example often the case of ARB prevalence and antibiotic concentration in waters, or ARB prevalence in animals. Antibiotic use is also not monitored in many SSA countries, both in farms and human populations. Country-specific contextual characteristics are also often lacking, e.g. raw food consumption, hygiene related parameters or access to improved water. Additionally, we already mentioned that many knowledge gaps remain: little is known regarding antibiotic resistance reversibility after withdrawal of antimicrobials, the probabilities of acquisition following exposure through ingestion (for food or water) or contacts, or the efficiency of wastewater treatments or hygiene at limiting ARB persistence and multiplication (Chereau et al., 2017). On the one hand, this lack of precision about model parameters values results in a strong uncertainty of model estimates and large prediction intervals, which should be considered when using the results in a decision process. On the other hand, the availability of quantitative risk assessment tools such as our model, which dissect the involved processes and highlight variables of interest, may help countries to collect better data, which may also naturally come along as national AMR containment programs gain experience over time.

Second, and of importance, there is a scarcity of data on ARB carriage at hospital admission in the region, but from the data available, we assumed this to be high, and equal to the carriage prevalence in the community (before amplification due to community factors). This assumption may be realistic in some countries but not all of them. For instance, in an Indian study, ESBL-producing *Enterobacteriaceae* carriage at ICU admission was estimated at 92% (Azim et al., 2010). Better and detailed data on antibiotic use in hospitals are needed as well, especially considering that recent reports suggest high and often inappropriate antibiotic use in some SSA hospitals (Gandra et al., 2017).

Third, in order to make the model as simple as possible, we assumed that incidence rates of ARB acquisition from livestock contacts, meat consumption and water consumption were additive and independent, and that there were no interactions between these processes. The same assumption was made for incidence rates of ARB acquisition from hospital and community. This may not represent the full complexity of the situation: indeed livestock animals also drink contaminated water, and individuals with frequent livestock contacts may tend to eat meat more frequently.

However, we made this hypothesis to facilitate the interpretation of the model. More complexification may be added in the future when more data is made available in the different compartments and at their interfaces.

Fourth, when modelling ARB acquisition via water, we assumed that the presence of antibiotics in water systematically selected for ARB. However, this may not be true for all antibiotics. Indeed, some antibiotic residues can become inactive and therefore have limited impact on ARB prevalence. Moreover, we assumed that wastewater treatment would always tend to reduce ARB prevalence in water which may not be the case: some wastewater treatment may amplify certain antibiotic resistance genes even if the bacteria is removed.

Fifth, our food submodel may be incomplete. We didn't take into account ARB acquisition from natural products consumption in the model, as insufficient scientific knowledge and concrete information was available. However, a recent review by Hölzel *el al*. underlines that knowledge about the weight of this acquisition route is still very poor and suggests that for most bacteria, the risk of acquisition via natural products consumption is very low, especially compared with meat products (Holzel, Tetens, & Schwaiger, 2018). In addition, we assumed that cooking eradicated ARB in contaminated meat in 99% of cases. This assumption was based on available data on ESBL-PE, for which total elimination through cooking of previously contaminated meat was observed (Boonyasiri et al., 2014), but may not hold true for all bacterial species.

Lastly, it is important to highlight that resistance emergence or evolution was not considered here. The present model investigates the acquisition risk of potentially pathogenic ARB for humans from the selection and diffusion in the different reservoirs of an already existing resistant bacterium. The processes leading to the emergence of a novel ARB or the evolution of an existing one are still poorly known and quantified, making their modelling particularly challenging. Antibiotic exposure has been suggested to amplify this process, and several studies suggest that SSA, for the high rates of antibiotic use, are particularly at risk of emergence of new strains. Future studies should be designed to address that specific question. It is important to note that we did not either specifically model the transmission of antibiotic resistance genes on their own, e.g. carried by other species than the one of interest or mobile elements. Indeed, it can be assumed that such genes would be selected or eliminated through the same processes as ARB, and therefore one can expect that their diffusion risk would be correlated to the one estimated here.

4.3. Conclusions

To conclude, we propose here a framework allowing a quantitative risk assessment of AMR acquisition in Asia by taking in a One-Health perspective that accounts simultaneously for the human, animal and environmental sectors. This quantitative assessment, as opposed to earlier qualitative assessments, allows computing risk levels and their impacts more accurately. After careful parameterization for a specific country setting, it will also allow a quantitative assessment of the impact of potential control measures and provide better support for their prioritization. This illustrates the need for collecting high-quality data on antimicrobial use, hygiene practices and ARB prevalence, as model predictions are bound to be dependent on the quality of the available data.

One advantage of the model is its flexibility, as it can be used in a variety of ways, depending on available data or questions one wants to address. For instance, any of the sub-models may be run independently, rather than the entire model, when focusing on a specific aspect of AMR selection. The model may also be adapted to any bacterial species of choice.

We therefore hope that our model will prove useful for policymakers. In future work, a free software allowing users to run this model could be made available to program managers.

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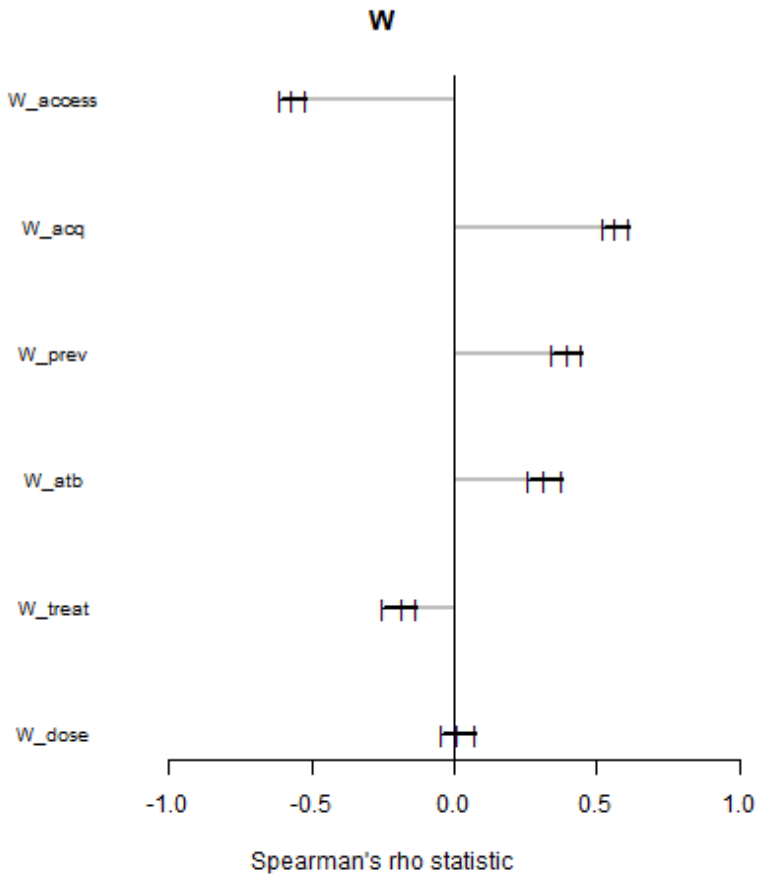
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APPENDIX

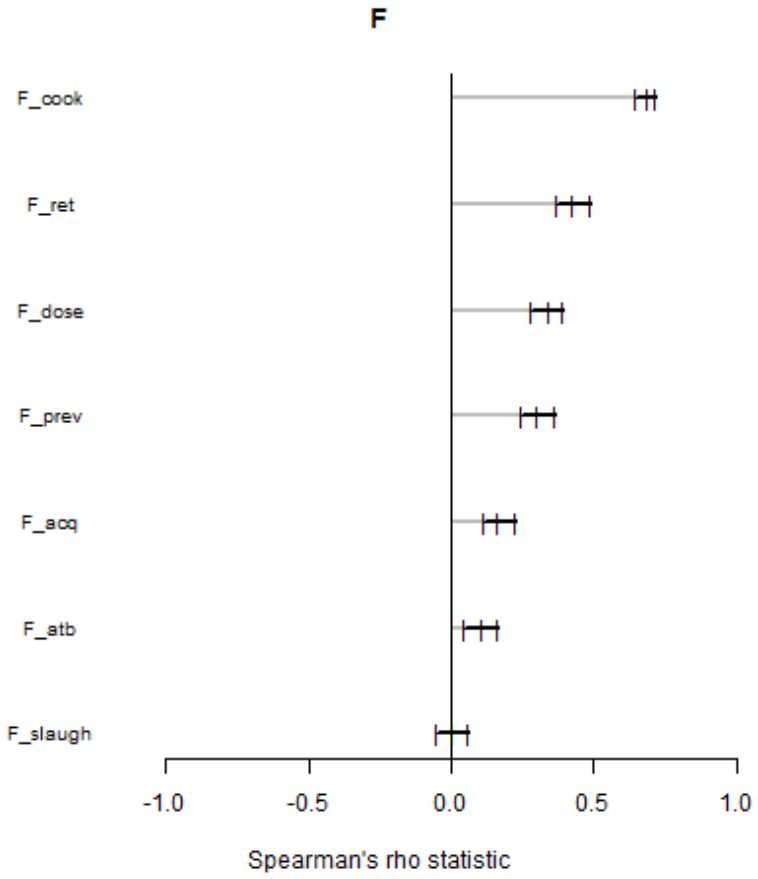
Supplementary Fig. S1 - Multivariate sensitivity analysis of the impact of the model variables on the risk at each sub-level.

Spearman rank correlation (mean, 95%CrI) between input variables and output risk calculated from 100,000 samples for:

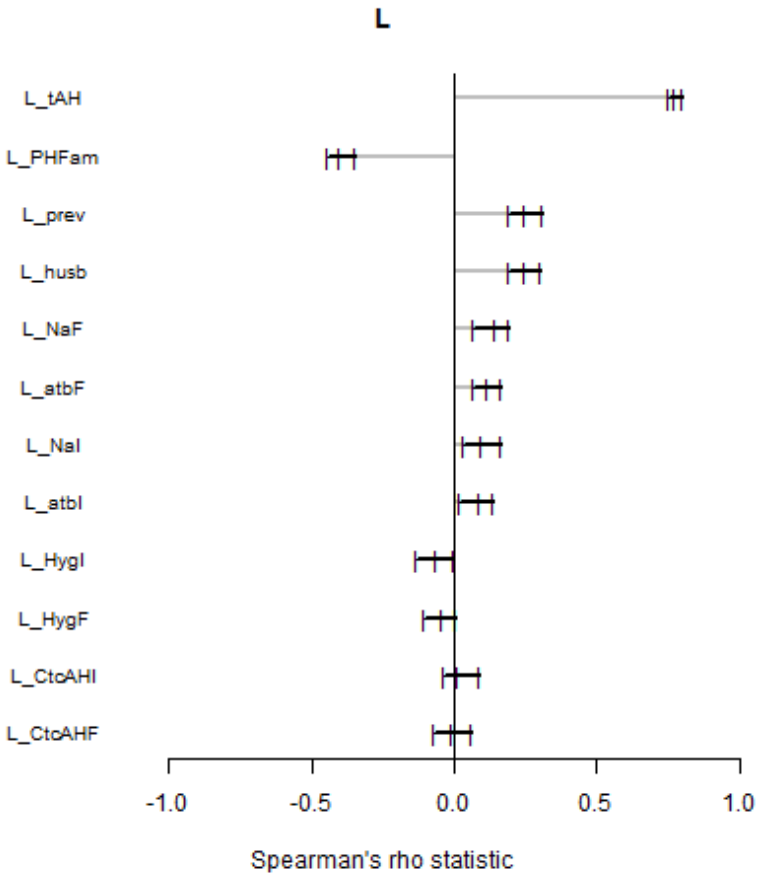
A) The water sub-model



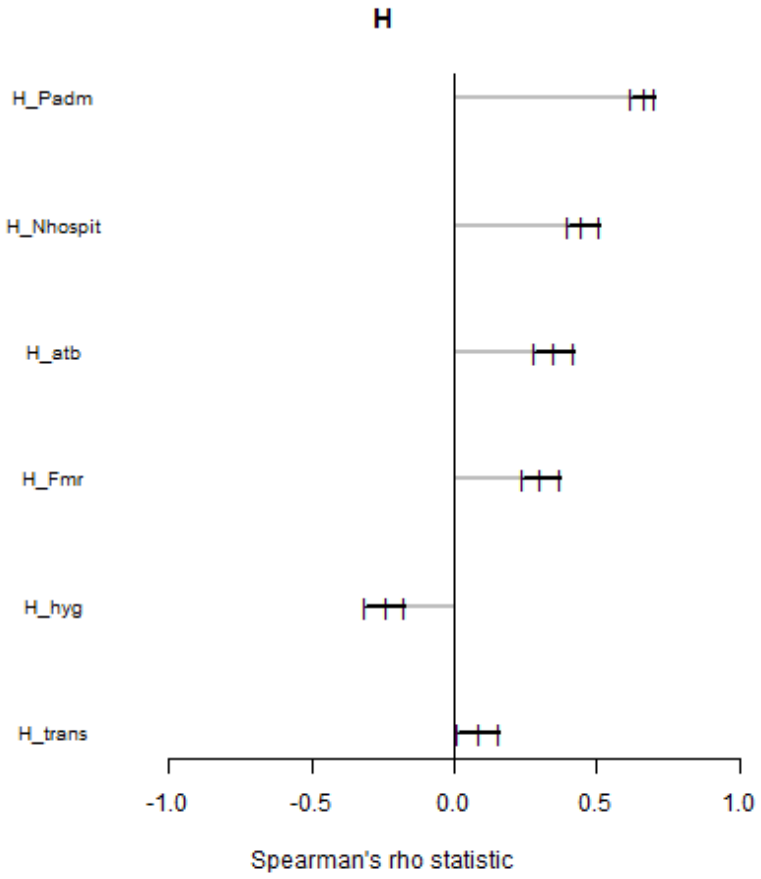
B) The food sub-model



C) The livestock contacts sub-model



D) The hospital sub-model



E) The community sub-model

