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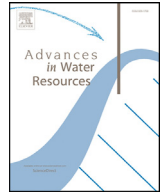
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Disease burden due to gastrointestinal infections among people living along the major wastewater system in Hanoi, Vietnam



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ABSTRACT

Background: Despite recent improvements of wastewater treatment capacities in urban areas of Hanoi, Vietnam, microbial pollution is still considerable. There is a paucity of burden estimates due to gastrointestinal infection in people living along the wastewater system, and among people who are in direct contact with the wastewater, such as farmers using wastewater in agriculture and aquaculture.

Methods: A quantitative microbial risk assessment (QMRA) was pursued focussing on four population groups characterised by different levels of exposure to wastewater: (i) workers maintaining the wastewater conveyance and treatment systems; (ii) urban farmers using wastewater from To Lich River; (iii) community members in urban areas exposed to flooding events in the districts of Hoang Mai and Thanh Tri; and (iv) peri-urban farmers in Thanh Tri district, where Red River water is used for agriculture and aquaculture. The QMRA was developed on the basis of measured concentration of *Escherichia coli* and *Salmonella* spp. and *Ascaris* spp. eggs in water samples. Published ratios between measured organisms and pathogenic strains of norovirus, rotavirus, *Campylobacter* spp., pathogenic *E. coli*, pathogenic *Salmonella* spp., *Cryptosporidium* spp. and *Ascaris lumbricoides* were employed to estimate annual risk of gastrointestinal infection and disease burden.

Results: The QMRA estimated a disease burden of 0.011 disability-adjusted life years (DALYs) per person per year in urban farmers, 0.006 DALYs for sanitation workers, 0.0005 DALYs for urban communities at risk of flooding events and 0.0004 DALYs for peri-urban farmers. Urban farmers had considerably higher incidence estimates for gastrointestinal disease episodes per year (2.0) compared to the other exposure groups (≤ 1.0).

Conclusions: Urban farmers using wastewater from To Lich River have a high gastrointestinal disease burden, which is about 100 times larger than the health-based targets for wastewater use set by the World Health Organization. These findings are of direct public health relevance and call for upgrading Hanoi's wastewater system to reduce microbial contamination. Finally, this study presents a first example on how to link QMRA to a sanitation safety planning (SSP) approach in an Asian context and its findings are interesting in the frame of Sustainable Development Goal (SDGs) #6.

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1. Introduction

In many urban centres in low- and middle-income countries (LMICs) large quantities of untreated or partially treated wastewater are discharged into the environment (Evans et al., 2012; Drechsel et al., 2015).

At the same time, there is an increasing demand of nutrients and energy in these contexts. This renders untreated wastewater – a resource that is rich in nutrients (e.g. nitrogen and phosphorus) – attractive for use in urban agriculture and aquaculture (Qadir et al., 2010; Hamilton et al., 2013). Indeed, planned use of treated wastewater in agriculture is projected to more than triple globally, from about 7 km³ in 2011 to 26 km³ in 2030 (Global Water Intelligence, 2014; AQUASTAT, 2015).

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Considerably larger volumes of only partially treated or untreated wastewater are used in agriculture (e.g. through diversion of water from wastewater receiving surface water bodies) (Fuhrmann et al., 2014, 2015; WHO, 2015). In Hanoi, for example, an estimated 660,000 farmers use wastewater for vegetable and rice farming and aquaculture on a surface area of approximately 44,000 ha (Raschid-Sally and Jayakody, 2008).

While the use of wastewater is an important livelihood strategy for poor urban farmers, there are important public health concerns (Winkler et al., 2016). In Southeast Asian cities, such as Hanoi, large quantities of insufficiently treated effluents contaminate surface waters and soils, resulting in high concentrations of pathogenic organisms and toxic chemicals (Kuroda et al., 2015; Fuhrmann et al., 2016a). This is explained by the fact that most of the 6.7 million people living in Hanoi rely on flush toilets directly connected to septic tanks from where the partially treated effluents are discharged into a complex network of drainage channels, which additionally receive effluents from industries (Fuhrmann et al., 2016b). Of note, faecal sludge from septic tanks is often informally discarded into the environment; in many cases directly into agricultural fields or ponds used for aquaculture (Bassan et al., 2015). In response, wastewater flows have been largely controlled by channelization of the main urban rivers, water gates and sedimentation pond systems to prevent flooding and to treat wastewater before use in agriculture and aquaculture (Nguyen and Parkinson, 2005; World Bank, 2013).

In a recent water quality assessment we found that, despite efforts to improve Hanoi's wastewater conveyance and treatment systems, water deriving from the wastewater channels being used in agricultural fields for irrigation is heavily contaminated with total coliforms (TC), *Escherichia coli* and *Salmonella* spp. (Fuhrmann et al., 2016a). Observed values were up to 110-fold above Vietnamese discharge limits for restricted agriculture and up to 260-fold above the World Health Organization (WHO)'s tolerable safety limits for unrestricted agriculture (Fuhrmann et al., 2016a). Additionally, a cross-sectional epidemiological survey revealed high prevalence of intestinal parasite infections in peri-urban and urban farmers (up to 30%), general communities (up to 10%) and workers maintaining the wastewater channels (10%) (Fuhrmann et al., 2016b). In the aforementioned study, the prevalence of self-reported diarrhoea episodes (recall period: 2 weeks) in adults in peri-urban communities, urban farmers and sanitation workers was 8–12%. These observations suggest that treatment efficacy of Hanoi's wastewater management system is insufficient in preventing microbial contamination. Consequently, people exposed to wastewater are at risk of gastrointestinal infection. However, prior research does not provide an estimate of the magnitude of the disease burden caused by specific pathogenic organisms (Katukiza et al., 2013; Machdar et al., 2013). The 2010 Global Burden of Disease (GBD) study estimated the burden caused by diarrhoeal diseases at 0.002 disability-adjusted life years (DALYs) per person per year (pppy) for an average Vietnamese, which is considerably higher than the WHO's health-based target for the exposure to wastewater (a tolerable additional burden between 10^{-6} and 0.0001 DALYs pppy is suggested) (WHO, 2006; Mara et al., 2010; Institute for Health Metrics and Evaluation, 2015). Context-specific disease burden estimates are, however, relevant to compare the impact of individual pathogens for different population groups, and to govern control measures in the wastewater system (Drechsel and Seidu, 2011).

Here we present a quantitative microbial risk assessment (QMRA), which is linked a sanitation safety planning (SSP) approach (WHO, 2015) with three specific objectives: (i) to estimate the disease burden due to gastroenteritis resulting from exposure to water-borne pathogens along the major wastewater system in Hanoi (Fuhrmann et al., 2016a); (ii) to validate model estimates

with findings obtained from a cross-sectional epidemiological survey (Fuhrmann et al., 2016b, 2016c); and (iii) to compare disease burden estimates with national and international standards and estimates (Institute for Health Metrics and Evaluation, 2015; Fuhrmann et al., 2016d).

2. Materials and methods

2.1. Ethical considerations

The study protocol was approved by the institutional research commission of the Swiss Tropical and Public Health Institute (Swiss TPH; Basel, Switzerland; reference no. FK #106). Ethical approval was obtained from the ethics committee in Basel, Switzerland (EKBB; reference no. 137/13) and the Hanoi School of Public Health (HSPH; Hanoi, Vietnam; reference no. 010/2014/YTCC–HD3). This study is registered with the clinical trial registry ISRCTN (identifier: ISRCTN13601686).

2.2. Study area

Hanoi is located in the north of Vietnam, situated at the Red River delta (geographical coordinates: 21°01'42.5" N latitude and 105°51'15.0" E longitude). The climate is sub-tropical with the main rainy season occurring from April to September and a year-round humidity of 80–90% (Climate-Data.org, 2015). The wastewater flows through the city, from north to south, along a topographic gradient of 20 m to 5 m above mean sea level in three main rivers: To Lich, Nhue and Red (Nguyen and Parkinson, 2005; Kuroda et al., 2015) (Fig. 1).

Our study focussed on three specific parts of Hanoi's wastewater system: (i) the To Lich River, which receives most of Hanoi's storm- and wastewater and the Yen Son treatment plant (operated by the Hanoi Sewerage and Drainage Company (HSDC)); (ii) two typical urban communes (Bang B and Tam Hiep) where wastewater from To Lich River is used for agriculture and aquaculture; and (iii) the peri-urban commune Duyen Ha where Red River water (considered as clean) is used in agriculture and aquaculture (Fuhrmann et al., 2016a, 2016b).

2.3. Hazard identification

The hazards considered for the QMRA are seven pathogenic organisms giving rise to gastroenteritis in Vietnam and elsewhere: two types of viruses (norovirus and rotavirus), three different bacteria (*Campylobacter* spp., *Salmonella* spp. and *E. coli*), one intestinal protozoan (*Cryptosporidium* spp.) and one species of soil-transmitted helminths (*Ascaris lumbricoides*) (Becker et al., 2013; Katukiza et al., 2013; Barker et al., 2014; Gibney et al., 2014; Fuhrmann et al., 2016d). These pathogens are characterised by faecal-oral transmission, can persist for weeks or months in the environment and are difficult to inactivate with conventional wastewater treatment processes such as those applied in Hanoi (Kuroda et al., 2015; Fuhrmann et al., 2016a). Our selection is further justified on the following grounds:

- Rotavirus is one of the leading cause of childhood diarrhoea (Bodhidatta et al., 2007).
- Norovirus is the major cause of diarrhoeal disease in adults and its secondary attack rate is known to be high causing epidemic situation (Barker, 2014; Mok et al., 2014).
- *Campylobacter* spp. are zoonotic bacteria that cause campylobacteriosis, with *Campylobacter jejuni* being a common cause of diarrhoea in LMICs (Kaakoush et al., 2015).
- *E. coli* belongs to the normal gastrointestinal microflora of warm-blooded animals and humans, whilst different types of

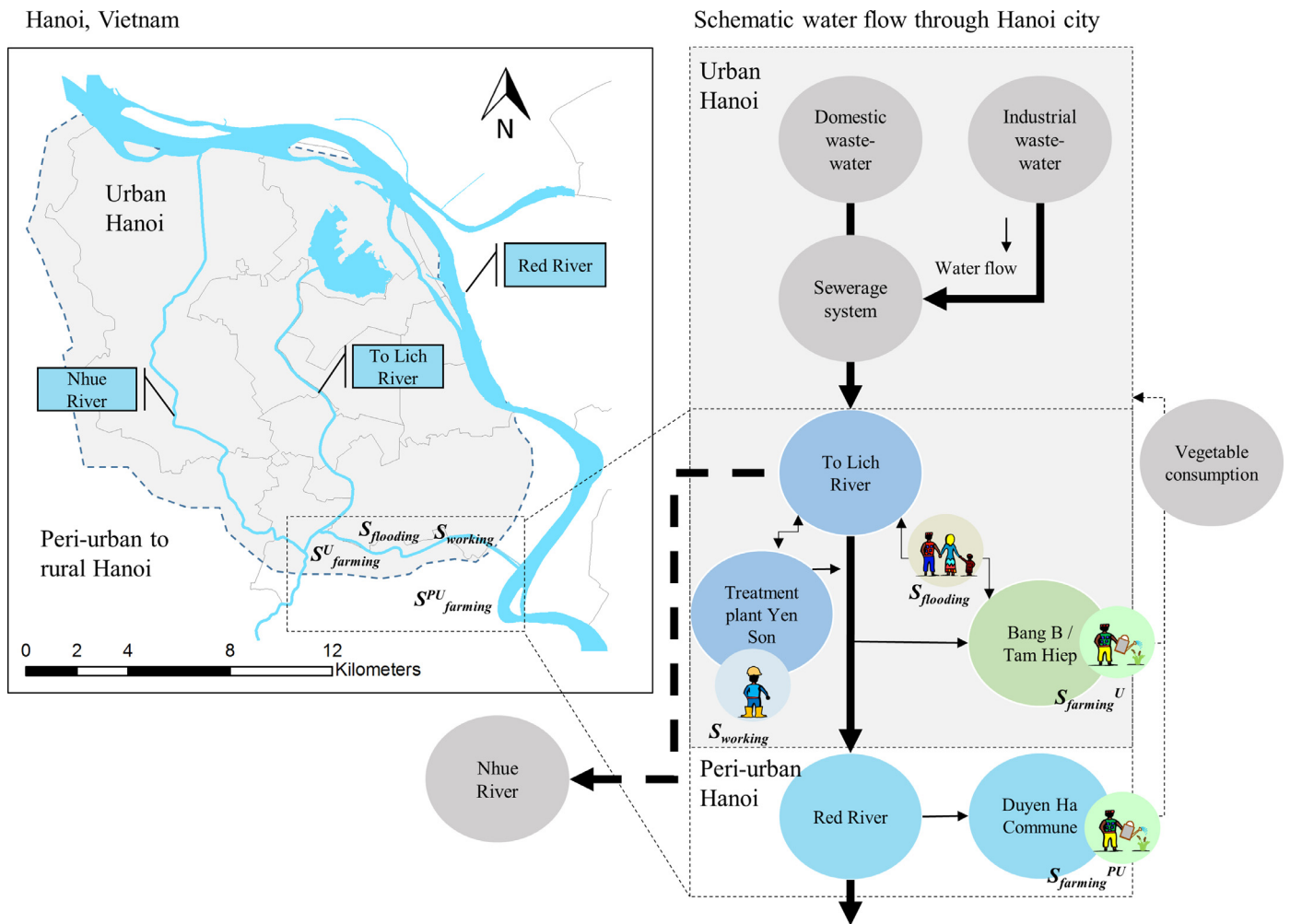


Fig. 1. Schematic flow of Hanoi's main wastewater system, with indication of the four exposure scenarios within the study areas ($S_{flooding}$, $S_{working}$, $S_{farming}^U$ and $S_{farming}^{PU}$) and potential exposure outside the scope of this study (i.e. contact to Nhue River water and vegetable consumption).

E. coli (e.g. enterotoxigenic *E. coli*, enteroinvasive *E. coli* and enterohemorrhagic *E. coli*) have been associated with diarrhoeal disease or even worse public health impact such as hemolytic uremic syndrome (HUS) (Okeke, 2009). As a simplification for the current QMRA, we refer to pathogenic *E. coli* that sums up all diarrhoea causing *E. coli*, whilst using the dose-response relation for probability of illness as derived for *E. coli* O157:H7.

- *Salmonella* spp. have more than 2,500 sero-groups; yet, of concern for human health are only *S. typhi* and *S. para-typhi* A, B and C, and the enteric *Salmonella* strains (Kariuki et al., 2015). As a simplification for the current QMRA, we refer to pathogenic *Salmonella* spp., which includes the diarrhoea causing *Salmonella* spp. *S. typhi*, *S. para-typhi* A, B and C, *S. Enteritidis* and *S. Typhimurium*.
- *Cryptosporidium* spp. is a zoonotic intestinal protozoon that can result in severe health implication in children and immunocompromised individuals (e.g. HIV-positive people).
- *A. lumbricoides* is the most widespread soil-transmitted helminth and is highly endemic in Vietnam. Parasite eggs are known to persist in the environment longer than any of the other soil-transmitted helminth species (Brooker et al., 2009).

2.4. Exposure assessment

The exposure scenarios for the QMRA are based on information derived from a cross-sectional survey, consisting of a questionnaire

survey and examination of stool samples from 618 people in the districts of Hoang Mai and Thanh Tri (Fuhrmann et al., 2016b). The results of the cross-sectional survey were used to obtain mode and frequency of exposure to wastewater and compare prevalence of parasitic infections and self-reported diarrhoea (recall period: 2 weeks) with estimates taking from the QMRA. As the focus of the model was to determine direct contact to contaminated water (considering all modes of pathogen transmission where contaminated water can be swallowed in the respective exposure scenario), the QMRA only included accidental ingestion of contaminated water as an exposure pathway. Other potential exposure pathways were excluded, such as: (i) ingestion of contaminated soil, dermal contact, inhalation and drinking of potentially contaminated water (lack of data); (ii) consumption of contaminated food crops (no data on degree of contamination of food crops); and (iii) exposure to contaminated water used for bathing or washing clothes (uncommon local practice).

Four exposure scenarios along the three selected study areas (To Lich River, wastewater use and Red River) were developed and assumptions about exposure groups, number of people exposed, exposure frequency and volume of ingested water were made (Figs. 1 and 2).

Exposure to water from To Lich River:

- **Scenario 1 ($S_{flooding}$):** Urban communities (all age groups) in Bang B and Tam Hiep living in close proximity to the To Lich

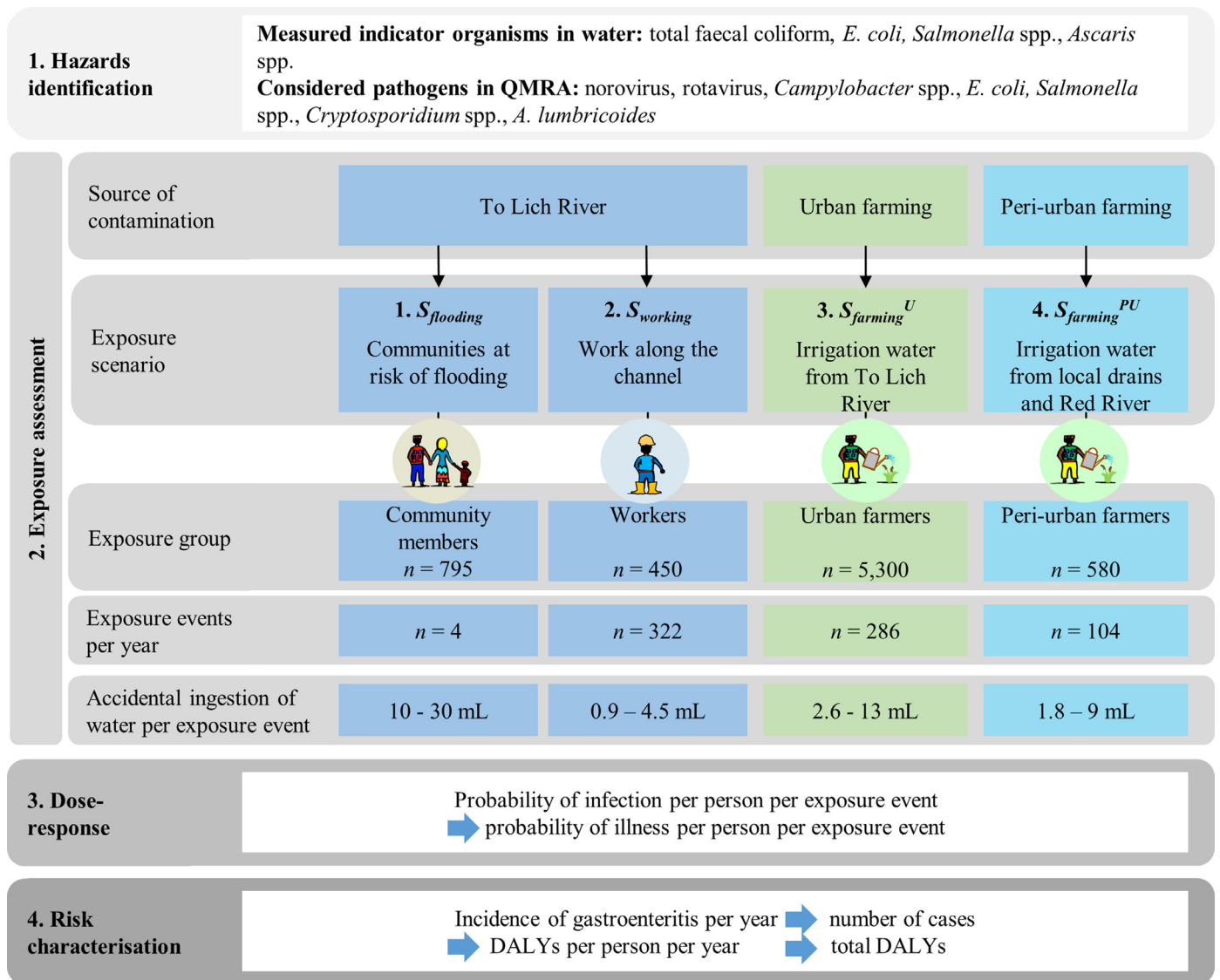


Fig. 2. Exposure scenarios (S_{flooding} , S_{working} , S_{farming}^U and S_{farming}^{PU}) considered in the quantitative microbial risk assessment (QMRA) to estimate the burden of norovirus, rotavirus, *Campylobacter* spp., *Escherichia coli* O157:H7, *Salmonella* spp., *Cryptosporidium* spp. and *Ascaris lumbricoides* along the major wastewater system in Hanoi.

River are prone to flooding events. For instance, 5% of the people living in these communities reported to be at risk of flooding events (i.e. 795 out of 15,900 people) (Fuhrmann et al., 2016b). According to HSDC, four flooding events occurred during the rainy season in 2013; the year before our epidemiological survey (Fuhrmann et al., 2016b). During a flooding event, ingestion of water due to unintentional immersion is assumed to range between 10 and 30 mL (McBride et al., 2013).

- **Scenario 2 (S_{working}):** There are 450 registered workers employed by the HSDC who are in charge of the maintenance of the To Lich River and the operation of the wastewater treatment plants (Yen Son). On average, a worker is on duty 322 days per year. Most of the workers wear gloves (91%), which we considered as a proxy for the level of awareness and preparedness to avoid accidental ingestion of contaminated water (WHO, 2006; Fuhrmann et al., 2016d). It was assumed that the worst case scenario (an accidental ingestion of 10–50 mL of wastewater per working day) was reduced to ingestion of 0.9–4.5 mL per working day (WHO, 2006; Labite et al., 2010; Mara and Bos, 2010).

Exposure to water use from To Lich River in agriculture fields of urban farming communes in Hanoi:

- **Scenario 3 (S_{farming}^U):** Urban farmers living in Bang B village or Tam Hiep commune using wastewater from To Lich River were selected for the model. One third of the community (an estimated 5,300) are involved in urban farming (mainly rice, morning glory, neptunia and watercress) or aquaculture. Thus, the likelihood of accidental ingestion of water is considerable. On average, farmers in Bang B village and Tam Hiep commune reported to work 338 days per year in flooded agricultural fields and they are in contact with irrigation water on a daily basis. Three out of four workers (74%) wear gloves, which we considered as a proxy for the level of awareness and preparedness to avoid accidental ingestion of contaminated water (WHO, 2006; Fuhrmann et al., 2016d). It was assumed that the worst case scenario (an accidental ingestion of 10–50 mL of wastewater per working day) was reduced to ingestions between 2.6 mL and 13 mL per working day (WHO, 2006; Labite et al., 2010; Mara and Bos, 2010).

Exposure to water used from Red River in agriculture fields of peri-urban farming communes in Hanoi:

- **Scenario 4 ($S_{farming}^{PU}$):** A typical peri-urban farming community living in Duyen Ha commune, 10 km away from the outskirts of Hanoi. Farmers using the irrigation water from Red River, wells or local drains, which are not contaminated with the city's wastewater but contaminated with household effluents. About 38% of the people work in agriculture (i.e. 580 urban famers). On average, farmers reported to work 338 days per year, though, fields are irrigated only every second day. 82% of the workers wear gloves, which we considered as a proxy for the level of awareness and preparedness to avoid accidental ingestion of contaminated water (WHO, 2006; Fuhrmann et al., 2016d). It was assumed that the worst case scenario (an accidental ingestion of 10–50 mL of wastewater per working day) was reduced to ingestions between 1.8 mL and 9 mL per working day (WHO, 2006; Labite et al., 2010; Mara and Bos, 2010).

2.5. Measurements of pathogens along the wastewater system

Water quality was tested for *E. coli*, TC, *Salmonella* spp. and helminth eggs between April and June 2014 (Fuhrmann et al., 2016a). The ratio between measured pathogens (p_{path}) and *E. coli* is assumed to vary between 10^{-6} and 10^{-5} (rotavirus, norovirus and *Campylobacter* spp.) or between 10^{-7} and 10^{-6} (*Cryptosporidium* spp.). The ratio between pathogenic and non-pathogenic strains of *E. coli* and *Salmonella* spp. (p_{path}) is assumed to vary between 7.6×10^{-4} and 1×10^{-2} (Shere et al., 2002; WHO, 2006; Soller et al., 2010; Barker et al., 2014; Hynds et al., 2014). For *Ascaris* spp. it is assumed that each egg detected represents an *A. lumbricoides* ($p_{path} = 1$, not considering the occurrence of other helminth species such as, for example, *A. suum*) (Mara and Sleight, 2010).

2.6. QMRA structure, implementation and analysis

Our QMRA approach has been described elsewhere (Fuhrmann et al., 2016d). We adhered to the WHO 2006 guidelines and the improved Karavarsamis–Hamilton method to determine annual disease and infection risks (WHO 2006; Karavarsamis and Hamilton 2010; Mara et al., 2010). As summarised in Table 1, spatial and temporal variability of the number of colony forming unit (CFU) *E. coli* and *Salmonella* spp., we fitted normal distributions to the log-transformed enumeration data on concentration in the water (C_{water}) (Fuhrmann et al., 2016a). A maximum likelihood estimation (MLE) method was used, allowing inclusion of censored data and accounting for the abundance, while considering the measured prevalence of the indicator bacteria in the water along the four systems (Lorimer and Kiermeier, 2007), in Excel 2013 (Microsoft Corporation, Redmond; WA, USA). As a result, the data fitting provided estimates for the true prevalence of contaminated water samples, and the distribution of concentrations in these contaminated samples. For *Ascaris* spp. eggs, this approach is not possible as only 17 out of 216 samples were positive. Hence, with $p = 0.08$ a positive count is expected, between 1 and 100 eggs/L, which is included with uniform distribution on a log scale (Fuhrmann et al., 2016a). Project evaluation and review techniques (PERT) distributions are fitted to minimum, most likely and maximum ratio of pathogen concentration per *E. coli* (p_{path}) for rotavirus, norovirus, *Campylobacter* spp. and *Cryptosporidium* spp. Uniform distribution were fitted to *E. coli* and *Salmonella* spp. ratio of pathogen concentration per measured *E. coli* and *Salmonella* spp. (WHO, 2006; Katukiza et al., 2013). This is implemented in the model by assuming that a fraction p_{path} of the ingested volumes of water consists of a pathogenic strain of the bacterial species. PERT distributions are also fitted to assumed minimum, most likely and maximum

ingestion rates (volume (V) in mL water) per exposure event. In a Monte Carlo simulation, values are sampled for these three variables and the ingested amount of pathogens (dose; d) is calculated as:

$$d = C_{water} \times p_{path} V \quad (1)$$

The variation in C_{water} is implemented as variability per exposure event, the variation in p_{path} and V is implemented as variability per person (i.e. for practical reasons it had the same value for all exposure events for one person in one iteration of the Monte Carlo simulation). As ingested bacteria are discrete units, assumed to be homogeneously distributed in the water, ingested doses are assumed to be Poisson distributed ($d \sim \text{Poisson}(d)$) as e.g. in Nauta et al. (2012).

Doses (d) are used as input in the dose-response relations to obtain the probability of illness $P_{ill}(d)$ (Eqs. 1 to 6). Monte Carlo simulations are performed for 100,000 iterations using @Risk, version 6 (Palisade Corporation; Newfield, NY, USA), where one iteration simulates all the n exposure events (n different doses d) and associated $P_{ill}(d)$ of one person in a year. The expected frequency of illness for a person per year (which, in our approach, might be above one) can be calculated as the sum of the n values of $P_{ill}(d)$ obtained (without considering immunity) (Haas et al., 2014). Model outputs are presented as number of cases per year, DALYs ppy and total DALYs per year (according to published burden estimate for gastroenteritis and fatality rates and adapted to the average life expectancy of 72 years in Vietnam (Salomon et al., 2012; Gibney et al., 2014).

2.7. Dose-response models

The same dose-response models for the various pathogens are used as described elsewhere (Fuhrmann et al., 2016d) to determine the relationship between quantity of exposure (i.e. number of organism ingested) and the effective health outcome (i.e. infection and illness) (Haas et al., 2014). For the QMRA, Beta-Poisson dose-response models for rotavirus, *Campylobacter* spp., pathogenic *E. coli*, pathogenic *Salmonella* spp. and *A. lumbricoides* were employed (Haas et al., 1999, 2014; Teunis and Havelaar, 2000; Teunis et al., 2008a; McBride et al., 2013), as follows:

$$P_I(d) = 1 - \left[1 + \left(\frac{d}{\beta} \right) \right]^{-\alpha} \quad (2)$$

With a median infectious dose defined as

$$N_{50} = \beta(2^{1/\alpha} - 1) \quad (3)$$

For norovirus, a hypergeometric function was used (Teunis et al., 2008b). We employed an approximation for the mean probability of infection (Haas, 2002) of the Beta-Poisson dose-response model:

$$P_I(d) = 1 - \frac{\Gamma(\alpha + \beta)\Gamma(d + \beta)}{\Gamma(\alpha + \beta + d)\Gamma(\beta)} \quad (4)$$

where $\Gamma(\cdot)$ represents Eulers gamma function (McBride et al., 2013). For *Cryptosporidium* spp., an exponential model was used (Westrell et al., 2004; de Man et al., 2013; McBride et al., 2013).

$$P_I(d) = 1 - (1 - r)^d \quad (5)$$

In brief, $P_I(d)$ represents the probability of infection, d is a single dose of the pathogen, whereas the pathogen infectivity constants α , β and r characterise the dose-response relationship. To account for the proportion of infections that turn into symptomatic cases ($P_{ill}(d)$), we used for each pathogen a constant value (λ) (i.e. illness to infection ratio):

$$P_{ill}(d) = P_I(d) \times \lambda \quad (6)$$

Table 1 (see also Section 2.8) provides values used in the QMRA for each pathogen.

Table 1

QMRA model assumptions used to estimate the burden of gastrointestinal infections among people living along the major wastewater system in Hanoi, Vietnam.

Description	Unit	Distribution and/or value(s)	Reference(s)
<i>(C_{water})</i> Concentrations in water To Lich River			(Fuhrmann et al., 2016a)
<i>Escherichia coli</i>	log ₁₀ (CFU/100 mL)	Normal (6.6;0.18)*	
<i>Salmonella</i> spp.	log ₁₀ (CFU/100 mL)	Normal (3.0;0.2)*	
<i>Ascaris</i> spp.	log ₁₀ eggs/1 L	Uniform (0;1.4)**, prevalence = 0.08	
<i>(C_{water})</i> Wastewater-fed agricultural fields in Bang B and Tam Hiep			
<i>Escherichia coli</i>	log ₁₀ (CFU/100 mL)	Normal (6.0;0.7)*	
<i>Salmonella</i> spp.	log ₁₀ (CFU/100 mL)	Normal (2.0;0.6)*	
<i>Ascaris</i> spp.	log ₁₀ eggs/1 L	Uniform (0;1.4)**; prevalence = 0.08	
<i>(C_{water})</i> Drainage system Duyen HA			
<i>Escherichia coli</i>	log ₁₀ (CFU/100 mL)	Normal (5.4;0.5)*	
<i>Salmonella</i> spp.	log ₁₀ (CFU/100 mL)	Normal (2.6;0.6)*	
<i>Ascaris</i> spp.	log ₁₀ eggs/1 L	Uniform (0;1.4)**, prevalence = 0.08	
<i>(P_{path})</i> Ratio between indicator and pathogenic organisms			
<i>A. lumbricoides</i> to <i>Ascaris</i> spp.	Eggs/Eggs	Point estimate = 1	(Mara and Sleight, 2010)
<i>Campylobacter</i> spp. to <i>E. coli</i>	CFU/CFU	PERT (0.1;0.55;1)*** per 10 ⁵ <i>E. coli</i>	(WHO, 2006)
<i>Cryptosporidium</i> spp. to <i>E. coli</i>	CFU/CFU	PERT (0.01;0.055;0.1)*** per 10 ⁵ <i>E. coli</i>	
Pathogenic <i>E. coli</i> O157:H7 to <i>E. coli</i>	CFU/CFU	Uniform (7.6 × 10 ⁻⁴ ; 1 × 10 ⁻²)**	Shere et al., 2002; Soller et al., 2010; Hynds et al., 2014
Norovirus to <i>E. coli</i>	CFU/CFU	PERT (0.1;0.55;1)*** per 10 ⁵ <i>E. coli</i>	(WHO, 2006)
Rotavirus to <i>E. coli</i>	CFU/CFU	PERT (0.1;0.55;1)*** per 10 ⁵ <i>E. coli</i>	(Fuhrmann et al., 2016d; Katukiza et al., 2013)
Pathogenic <i>Salmonella</i> to <i>Salmonella</i> spp.	CFU/CFU	Uniform (7.6 × 10 ⁻⁴ ; 1 × 10 ⁻²)**	(Shere et al., 2002; Soller et al., 2010; Hynds et al., 2014)
<i>(V)</i> Volume ingested per exposure event for each scenario			
<i>S_{flooding}</i>	mL	PERT (10;20;30)***	(Katukiza et al., 2013; Fuhrmann et al., 2016d)
<i>S_{working}</i>	mL	PERT (0.9;2.7;4.5)***	(Labite et al., 2010)
<i>S_{farming^U}</i>	mL	PERT (2.6;7.8;13)***	(Labite et al., 2010)
<i>S_{farming^{PU}}</i>	mL	PERT (1.8;5.4;9)***	(Katukiza et al., 2013; Fuhrmann et al., 2016d)
Dose-response models			
<i>A. lumbricoides</i>		Point estimate: α = 0.0104; N ₅₀ = 859	(Mara and Sleight, 2010)
<i>Campylobacter</i> spp.		Point estimate: α = 0.145; N ₅₀ = 896	(Medema et al., 1996)
<i>Cryptosporidium</i> spp.		Point estimate: r = 0.0042	(Haas et al., 1999)
<i>E. coli</i> O157:H7		Point estimate: α = 0.49; N ₅₀ = 596,000	(Teunis et al., 2008a)
Norovirus		Point estimate: α = 0.04; β = 0.055;	(Teunis et al., 2008b)
Rotavirus		Point estimate: α = 0.253; N ₅₀ = 6	(Teunis and Havelaar, 2000)
<i>Salmonella</i> spp.		Point estimate: α = 0.3126; N ₅₀ = 23,600	(Haas et al., 1999)
<i>(λ)</i> Illness to infection ratio			
<i>A. lumbricoides</i>		Point estimate: 0.39	(Mara and Sleight, 2010)
<i>Campylobacter</i> spp.		Point estimate: 0.3	(Machdar et al., 2013)
<i>Cryptosporidium</i> spp.		Point estimate: 0.79	(Machdar et al., 2013)
Pathogenic <i>E. coli</i>		Point estimate: 0.35	(Machdar et al., 2013)
Norovirus		Point estimate: eta = 0.00255; r = 0.086	(Teunis et al., 2008b)
Rotavirus		Point estimate: 0.5	(Barker, 2014)
Pathogenic <i>Salmonella</i> spp.		Point estimate: 1	(Amha et al., 2015)
<i>(n)</i> Number of exposure events per year			(Fuhrmann et al., 2016b)
<i>S_{flooding}</i>		Point estimate: 4	
<i>S_{working}</i>		Point estimate: 322	
<i>S_{farming^U}</i>		Point estimate: 286	
<i>S_{farming^{PU}}</i>		Point estimate: 104	
<i>(Pop_E)</i> Population at risk per exposure scenario			(Fuhrmann et al., 2016b)
<i>S_{flooding}</i>	People	Point estimate: 795	
<i>S_{working}</i>	People	Point estimate: 450	
<i>S_{farming^U}</i>	People	Point estimate: 5,300	
<i>S_{farming^{PU}}</i>	People	Point estimate: 580	
<i>(DALY_h)</i> Disease burden per pathogenic organisms; disability-adjusted life years (DALYs) calculation is indicated in Table 2			
<i>A. lumbricoides</i>	DALYs/case	Point estimate: 0.0029	
<i>Campylobacter</i> spp.	DALYs/case	Point estimate: 0.0053	
<i>Cryptosporidium</i> spp.	DALYs/case	Point estimate: 0.0022	
Pathogenic <i>E. coli</i>	DALYs/case	Point estimate: 0.0013	
Norovirus	DALYs/case	Point estimate: 0.0008	
Rotavirus	DALYs/case	Point estimate: 0.0032	
Pathogenic <i>Salmonella</i> spp.	DALYs/case	Point estimate: 0.0719	

* Normal distribution (mean; standard deviation); **Uniform distribution (min; max); ***Project evaluation and review techniques (PERT) (min; most likely; max)

2.8. Risk characterisation

2.8.1. Incidence: the number of cases per year

Risk characterisation was done as described elsewhere (Fuhrmann et al., 2016d). When assuming that each exposure event i is independent and that there is no acquired immunity after an infection, with $P_{ill/h}(d_i)$ representing the probability of

illness, which is a function of the ingested dose d_i at exposure event i for each of the seven pathogens (or hazards) h (Eq. 6), then for an average of n_h exposures to the hazard per person per year, with population size Pop_E , the expected number of cases is

$$Cases_h = \sum_{i=1}^{n_h \times Pop_E} P_{ill, h}(d_i) \quad (7)$$

The incidence estimate for pathogen h is

$$Inc_h = \frac{Cases_h}{n_h \times Pop_E} \quad (8)$$

The combined incidence estimate, Inc_{comb} (episodes of gastroenteritis per year), for all seven pathogens h is defined as

$$Inc_{comb} = \sum_{all\ h} \frac{Cases_h}{n_h \times Pop_E} \quad (9)$$

2.8.2. Estimation of disease burden

The disease burden due to human exposure is expressed in DALYs. This metric combines morbidity (years lived with disability) and premature death (years of life lost) (Murray et al., 2012). For each pathogen h , DALYs per case of gastrointestinal illness ($DALY_h$) are calculated as the sum of the product of the probability of developing disease symptom j (i.e. j = mild, moderate and severe diarrhoea or death) given the illness occurs, relative frequency of the symptom (f_j), duration of the developed symptom in years (D_j) and the respective severity factor (S_j) (Salomon et al., 2012):

$$DALY_h = \sum_j f_j \times D_j \times S_j \quad (10)$$

Mortality is calculated according to the average life expectancy at birth in Vietnam of 72 years (Katukiza et al., 2013). Note that sequelae such as HUS, Guillain-Barré syndrome, reactive arthritis or irritable bowel syndrome are not considered in the model. The total disease burden ($Total_{DALYs,h}$) per hazard is the product of cases ($Cases_h$) and DALYs per pathogen:

$$DALYs_h = Cases_h \times DALY_h \quad (11)$$

The total disease burden for all hazards together is

$$Total_{DALYs} = \sum_h Cases_h \times DALY_h \quad (12)$$

3. Results

3.1. Incidence of gastroenteritis

The combined estimated incidence (Inc_{comb}) for gastroenteritis episodes per year due to the exposure to contaminated water was highest for urban farmers ($S_{farming}^U$), and sanitation workers ($S_{working}$) who suffer, on average, 2.0 and 1.0 gastroenteritis episodes per person per year (Fig. 3, Table 3). Incidence estimates were considerably lower for people exposed to flooding events ($S_{flooding}$) and peri-urban farmers ($S_{farming}^{PU}$) (>0.1 episodes per person per year for both groups) (Table 3). Most episodes were caused by rotavirus (1.5 episode per year), *E. coli* (0.6 episodes per year), *Campylobacter* spp. (0.4 episodes per year) and *Cryptosporidium* spp. (0.4 episodes per year). Considerably fewer episodes were caused by any of the other pathogens (<0.1 episodes per year).

3.2. Number of gastroenteritis cases per year

Among the 7,125 exposed people in the districts of Hoang Mai and Thanh Tri, a total of 11,073 cases of gastroenteritis caused by any of the seven pathogens were estimated due to exposure to wastewater for the four scenarios and the duration of one year (Fig. 3, Table 2). Gastrointestinal infection due to rotavirus, *E. coli* and *Campylobacter* spp. contributed most to the total cases (59%, 18% and 13%, respectively). Taken together, 95.0% of all cases were concentrated in the 5,300 urban farmers ($S_{farming}^U$: 10,511 cases).

3.3. Total disease burden per year

Across all 7,125 exposed people and four scenarios, our model estimated a burden of 62.6 DALYs per year due to exposure to wastewater in Hoang Mai and Thanh Tri district. The main responsible pathogens were *E. coli*, rotavirus and *Campylobacter* spp., accounting for 42%, 39% and 14% of the burden, respectively. Urban farmers ($S_{farming}^U$) were most vulnerable with a burden of 59.5 DALYs.

3.4. Disease burden per person per year

Combined DALYs pppy for all scenarios (summed-up for the seven pathogen and all exposed individuals) were far above the revised WHO reference level of 0.0001 DALYs pppy (Table 1). The highest disease burden was estimated at 0.011 DALYs pppy in urban farmers ($S_{farming}^U$), followed by sanitation workers ($S_{working} = 0.0057$ DALYs pppy), urban communities at risk of flooding events ($S_{flooding} = 0.0005$ DALYs pppy) and peri-urban farmers ($S_{farming}^{PU} = 0.0004$ DALYs pppy). In terms of different pathogens, *E. coli*, rotavirus and *Campylobacter* spp. had the largest share with 0.0037, 0.0035 and 0.0013 DALYs pppy, respectively.

4. Discussion

4.1. Disease burden estimates and comparison with standards

Our estimated gastrointestinal disease burden among urban farmers and sanitation workers who are exposed to wastewater are 5.6- and 2.8-fold higher than the diarrhoea burden estimates for the average Vietnam citizen (0.002 DALYs pppy) (Institute for Health Metrics and Evaluation, 2015). The high number of cases and the resulting burden due to *E. coli*, rotavirus and *Campylobacter* spp. together cause most of the disease burden (88%), which is in line with prior QMRA investigations in Asia and Africa (Pham-Duc, 2012; Katukiza et al., 2013; Machdar et al., 2013; Fuhrmann et al., 2016d). To our knowledge, we present the first specific QMRA to estimate disease burden due to exposure to wastewater for high-risk groups in Southeast Asia. Compared to a prior study conducted in Kampala, Uganda, using the same methodology as presented here, the current estimates are considerably lower (e.g. the estimated burden for urban farmers in Hanoi was 0.011 DALYs pppy compared to 0.073 DALYs pppy in Kampala) (Fuhrmann et al., 2016d). Very high estimates were obtained by QMRA models with regard to people exposed to wastewater in a typical slum area in Kampala (15,015 people; burden 10,172 DALYs) (Katukiza et al., 2013) and an urban wastewater systems in Accra (286,833 people; burden 31,979 DALYs) (Labite et al., 2010). These differences might, at least partially, be explained by specific social-ecological contexts, pathogen spectrum, DALY estimates per pathogens (e.g. we excluded sequelae) and methodological differences (e.g. calculation of risk of illness).

4.2. Comparison of QMRA estimates with epidemiological survey data

Only few studies have compared QMRA estimates with diarrhoea episodes assessed in epidemiological surveys (Bouwknegt et al., 2014; Haas et al., 2014). We aimed to fill this gap, and hence, conducted a cross-sectional survey, assessed water quality and obtained data on self-reported diarrhoeal episodes with a recall period of 2 weeks (Fuhrmann et al., 2016b). Extrapolating the self-reported 2-week diarrhoeal prevalence rate to 1 year (52 weeks, considering no seasonality), the annual incidence would be slightly higher compared to the combined incidence rates of all seven pathogens estimated in the QMRA (i.e. 2.6 versus 2.0 in urban farmers; 2.3 versus 0.09 in urban community members at

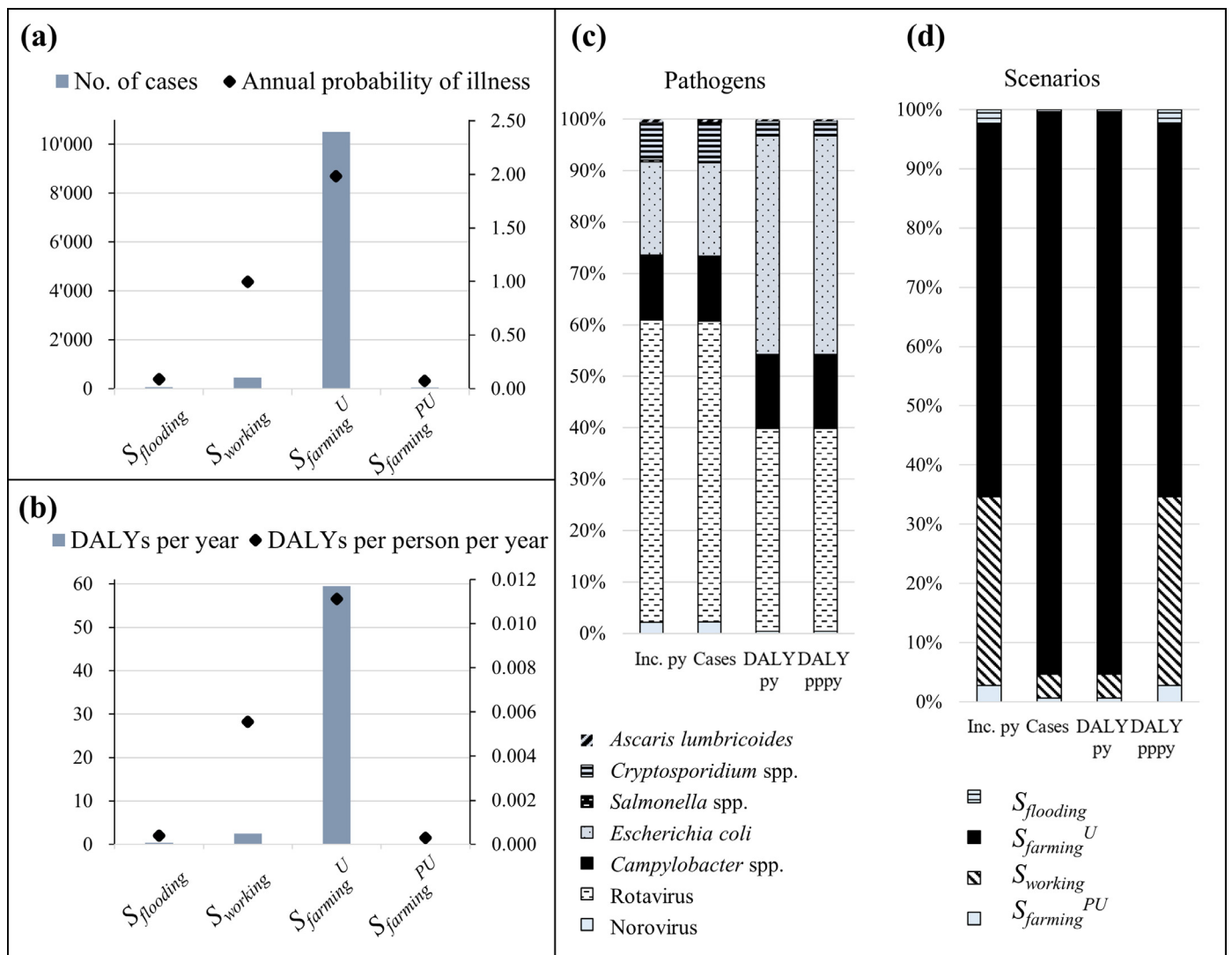


Fig. 3. Estimated number of cases, annual incidence of gastroenteritis per year (Inc py), disability-adjusted life years (DALYs) per year (py) and per person per year (pppy); (a) and (b) showing estimates of the respective outcomes per $S_{flooding}$, $S_{working}$, $S_{farming}^U$ and $S_{farming}^{PU}$; (c) and (d) are indicating the contribution of individual pathogens and scenarios, respectively, to the total estimated numbers per outcome along the major wastewater system in Hanoi, Vietnam.

risk of flooding events; 2.1 versus 1.0 in sanitation workers; and 1.0 versus 0.07 in peri-urban farmers). These obtained differences for urban farmers, communities and sanitation workers might be explained by additional risk factors for diarrhoeal disease, which drive the higher estimate (e.g. contaminated food crops, drinking water, human-to-human transmission, heavy metals or pesticides). Hence, future QMRA or chemical risk assessment should account for such factors, along with the potential effect of vulnerability and potentially acquired immunity to infectious agents within the exposed population groups in LMICs (Minh et al., 2004; Holm et al., 2010; Mok et al., 2014).

Further, when focusing on helminthiasis, the QMRA estimated that 74 people would be infected with *A. lumbricoides* over the course of a year, with 71 cases among urban farmers. These low incidence rates for urban farmers (1.4% of total cases) are in line with our cross-sectional survey, which did not detect a single *A. lumbricoides* infection in farmers using wastewater. As deworming is done on a regular basis and a significant protective effect was found in our cross-sectional survey, this low incidence might indeed remain undetected in epidemiological surveys (Fuhrmann et al., 2016b). In the light of our findings, for further cross-comparison between epidemiological surveys and QMRA, a standardised way to assess

incidence and burden of diarrhoeal episodes and intestinal parasitic infections should be proposed and validated to make use of both tools. This statement can also be underlined by a similar comparison of QMRA estimates with findings from an epidemiological survey in Kampala (Fuhrmann et al., 2016b, 2016c).

4.3. Sensitivity analysis

A sensitivity analysis of the QMRA model employed here has been presented by Fuhrmann et al. (2016d). There is a considerable effect of different volumes of water accidentally ingested. Such accidental ingestion may not be very accurate, as it is highly dependent on individual behaviours, which are influenced by age, sex, educational attainment and socioeconomic status (WHO, 2006; Haas et al., 2014). Moreover, pathogen ratio for rotavirus, *E. coli* and *Campylobacter* have shown a considerable effect on the total number of gastroenteritis cases, as there is considerable difference in microbial contamination between seasons in urban wastewater systems this might have considerable effect on the number of cases (Ensink, 2006; Katukiza et al., 2013; Fuhrmann et al., 2015, 2016a). It is important to note that *E. coli* is secreted by humans and animals continuously, whereas pathogens

Table 2

Disease burden due to gastroenteritis expressed in disability-adjusted life years (DALYs) calculated by means of severity (mild, moderate, severe and fatal), probability and duration of the respective severity grade, stratified by pathogen.

Gastroenteritis		Severity weights					Reference
		Mild	Moderate	Severe	Fatal	Total DALYs	
DALYs per severity grade of gastroenteritis		0.06	0.20	0.28	1.00		(Salomon et al., 2012)
Norovirus	Probability	0.92	0.07	0.01	7.80×10^{-6}		(Gibney et al., 2014)
	Duration (days)	2.10	2.40	7.20			
	Duration (years)	0.01	0.01	0.02	72		
	DALYs	3.24×10^{-4}	9.56×10^{-5}	3.33×10^{-5}	4.23×10^{-4}	1.01×10^{-3}	
Rotavirus	Probability	0.85	0.10	0.05	3.37×10^{-5}		(Gibney et al., 2014)
	Duration (days)	4.90	7.10	7.70			
	Duration (years)	0.01	0.02	0.02	72		
	DALYs	6.94×10^{-4}	4.01×10^{-4}	2.96×10^{-4}	1.83×10^{-3}	3.82×10^{-3}	
Cryptosporidium spp.	Probability	0.86	0.12	0.02			(Gibney et al., 2014)
	Duration (days)	5.00	15.00	33.00			
	Duration (years)	0.01	0.04	0.09			
	DALYs	7.19×10^{-4}	1.02×10^{-3}	4.32×10^{-4}		2.17×10^{-3}	
Campylobacter spp.	Probability	0.80	0.18	0.02	6.72×10^{-5}		(Havelaar et al., 2000) (Gibney et al., 2014)
	Duration (days)	3.50	9.70	14.40			
	Duration (years)	0.01	0.03	0.04	72		
	DALYs	4.70×10^{-4}	9.72×10^{-4}	1.77×10^{-4}	3.64×10^{-3}	6.46×10^{-3}	
Pathogenic <i>Salmonella</i> spp.	Probability	0.21	0.66	0.14	1.26×10^{-3}		(Gibney et al., 2014)
	Duration (days)	2.50	6.00	12.00			
	Duration (years)	0.01	0.02	0.03	72		
	DALYs	8.61×10^{-5}	2.18×10^{-3}	1.27×10^{-3}	6.85×10^{-2}	9.43×10^{-2}	
Pathogenic <i>E. coli</i>	Probability	0.94	0.06	0.09	2.00×10^{-4}		(Katukiza et al., 2013)
	Duration (days)	5.60	10.70	16.20			
	Duration (years)	0.02	0.03	0.04	72		
	DALYs	8.80×10^{-4}	3.55×10^{-4}	1.12×10^{-3}	1.08×10^{-2}	1.32×10^{-2}	
<i>Ascaris lumbricoides</i>	Probability	0.95	0.05				(Barker et al., 2014)
	Duration (days)	35.0	28.0				
	Duration (years)	0.05	0.01				
	DALYs	2.90×10^{-3}	1.83×10^{-5}			2.92×10^{-3}	

are secreted only by a proportion of infected people over a short period of a few days. This might affect the *E. coli* to pathogen ratio change over time (Mara, 2004; Haas et al., 2014).

4.4. QMRA limitations

Our model framework has several limitations, which are offered for consideration. First, the estimates of the ingested volumes of water are based on literature values for certain human behaviours (Labite et al., 2010; Schets et al., 2011; Katukiza et al., 2013). Second, the dose-response models applied in our model are based on feeding studies (e.g. norovirus) or rely on epidemiological evidence (e.g. *Ascaris* spp.) collected in high-income countries (de Man et al., 2013; Barker et al., 2014). Third, in scenario 1 we do not differentiate between adults and children. Especially for rotavirus, burden is known to be substantially different between age groups (Mok and Hamilton, 2014). Fourth, the model excluded other exposure pathways such as dermal contact (e.g. hookworm and skin disease) and inhalation. It is reported that other water-borne pathogens such as hepatitis, cholera and adenoviruses occur in high prevalence and cause severe health implications (Karagiannis-Voules et al., 2015; Fuhrmann et al., 2016b). Fifth, partially acquired immunity due to exposure history or vaccination may result in lower estimates (Sunger and Haas, 2015). Sixth, the duration of a fatal case was assumed to be equal to the life expectancy at birth, which is likely to result in an overestimation of the burden estimates (Katukiza et al., 2013; Fuhrmann et al., 2016d). Finally, long-term sequelae is often contributing to a significant proportion of DALYs when assessing burden to intestinal pathogens in high-income countries, hence, for next QMRA in LMICs sequelae should be included (Havelaar et al., 2000).

5. Conclusions

Employing a QMRA approach, we found high incidence of water-borne pathogens among urban farmers in Hanoi who use wastewater in agriculture and aquaculture. The validation of the QMRA estimates with findings from epidemiological surveys showed that QMRA estimated incidence of gastroenteritis was considerably lower, which can be explained by additional transmission routes (e.g. food crops) which can result in gastroenteritis cases. The high incidence of gastrointestinal infections results in considerable disease burden, which is 5.6-fold higher in urban farmers compared to an average Vietnamese and more than hundred times above the revised WHO tolerable level of 0.0001 DALYs pppy. In turn, exposure to wastewater around Hanoi has considerable public health implications for these three population groups and call for actions, especially to bring down the burden due to *E. coli*, rotavirus and *Campylobacter* spp. infections.

Against this background, health-based targets should be set according to local idiosyncrasies after validation with epidemiological findings. For example, as a first step towards setting local targets could be the consideration of estimates provided by the Global Burden of Disease study 2010. These findings are especially interesting in the frame the Sustainable Development Goals (SDGs), as they address sustainable and safe wastewater reuse and recovery systems, from the point of generation to the point of disposal and (re)use for minimising adverse health impacts associated with water-borne disease, while maximising gains from safe wastewater use in agriculture and aquaculture in LMICs. Finally, the study provides a first example on how to link quantification of health risk using a QMRA to an SSP approach in an Asian context.

Table 3

QMRA estimates for annual probability of illness, number of cases per year, total DALYs per year, DALYs per person per year across all four exposure scenarios (S_{flooding} , S_{working} , S_{farming}^U and S_{farming}^{PU}) and seven pathogens along the major wastewater system in Hanoi, Vietnam.

Exposure scenario (n = exposed population)	S_{flooding} (n = 795)	S_{working} (n = 450)	S_{farming}^U (n = 5,300)	S_{farming}^{PU} (n = 580)	Total (n = 7125)
Incidence of gastroenteritis per year (I_{Ch_h})					
Norovirus	0.002	0.020	0.045	0.001	0.07
Rotavirus	0.051	0.597	1.160	0.041	1.85
<i>Campylobacter</i>	0.011	0.127	0.249	0.009	0.40
<i>E. coli</i>	0.016	0.180	0.361	0.013	0.57
<i>Salmonella</i> spp.	0.000	0.004	0.002	0.002	0.01
<i>Cryptosporidium</i>	0.006	0.069	0.153	0.005	0.23
<i>A. lumbricoides</i>	0.001	0.003	0.013	0.002	0.02
Total number	0.088	1.000	1.983	0.074	3.14
No. cases per year ($Cases_h$)					
Norovirus	2	9	237	1	248
Rotavirus	41	269	6,146	24	6,480
<i>Campylobacter</i>	9	57	1,321	5	1,392
<i>E. coli</i>	13	81	1,915	8	2,017
<i>Salmonella</i> spp.	0	2	12	1	15
<i>Cryptosporidium</i>	5	31	809	3	848
<i>A. lumbricoides</i>	1	1	71	1	74
Total number	70	450	10,511	43	11,073
DALYs per year ($Total_{\text{DALYs},h}$)					
Norovirus	0.00	0.01	0.24	0.00	0.25
Rotavirus	0.16	1.03	23.46	0.09	24.73
<i>Campylobacter</i>	0.06	0.37	8.53	0.03	8.99
<i>E. coli</i>	0.17	1.07	25.27	0.10	26.61
<i>Salmonella</i> spp.	0.00	0.00	0.01	0.00	0.02
<i>Cryptosporidium</i>	0.01	0.07	1.76	0.01	1.84
<i>A. lumbricoides</i>	0.00	0.00	0.21	0.00	0.22
Combined DALYs ($Total_{\text{DALYs}}$)	0.40	2.54	59.48	0.24	62.66
DALYs per person per year ($DALY_{\text{pppy},h}$)					
Norovirus	0.0000	0.0000	0.0000	0.0000	0.0000
Rotavirus	0.0002	0.0023	0.0044	0.0002	0.0035
<i>Campylobacter</i>	0.0001	0.0008	0.0016	0.0001	0.0013
<i>E. coli</i>	0.0002	0.0024	0.0048	0.0002	0.0037
<i>Salmonella</i> spp.	0.0000	0.0000	0.0000	0.0000	0.0000
<i>Cryptosporidium</i>	0.0000	0.0001	0.0003	0.0000	0.0003
<i>A. lumbricoides</i>	0.0000	0.0000	0.0000	0.0000	0.0000
Combined DALYs	0.0005	0.0057	0.0112	0.0004	0.0088

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