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Disease burden due to gastrointestinal pathogens in a wastewater system in Kampala, Uganda

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ABSTRACT

In wastewater systems in Kampala, Uganda, microbial contamination has increased over the past two decades. Those people who live or work along the Nakivubo channel and wetland and those who use the recreational areas along the shores of Lake Victoria are at an elevated risk of gastrointestinal infections. A quantitative microbial risk assessment (QMRA) was applied for five population groups, characterised by different levels of exposure to wastewater in the Nakivubo area, namely: (i) slum dwellers at risk of flooding; (ii) children living in these slum settlements; (iii) workers maintaining the drainage system or managing faecal sludge (sanitation workers); (iv) urban farmers; and (v) swimmers in Lake Victoria. The QMRA was based on measured concentrations of *Escherichia coli*, *Salmonella* spp. and *Ascaris* spp. eggs in wastewater samples. Published ratios between measured organism and pathogenic strains of norovirus, rotavirus, *Campylobacter* spp., pathogenic *E. coli*, pathogenic *Salmonella* spp., *Cryptosporidium* spp. and *Ascaris lumbricoides* were used to estimate annual incidence of gastrointestinal illness and the resulting disease burden. The QMRA estimated a total of 59,493 disease episodes per year across all 18,204 exposed people and an annual disease burden of 304.3 disability-adjusted life years (DALYs). Incidence estimates of gastrointestinal disease episodes per year were highest for urban farmers (10.9) and children living in slum communities (8.3), whilst other exposed groups showed lower incidence (<4.3). Disease burden per person per year was highest in urban farmers (0.073 DALYs) followed by sanitation workers (0.040 DALYs) and children in slum communities (0.017 DALYs). Our findings suggest that the exposure to wastewater is associated with public health problems, particularly children and adults living and working along the major wastewater and reuse system in Kampala. Our findings call for specific interventions to reduce the disease burden due to exposure to wastewater.

1. Introduction

Urban wastewater is often contaminated with pathogenic organisms, and thus puts people at risk of ill-health (Blumenthal and Peasey, 2002; McBride et al., 2013; Barker, 2014). Untreated wastewater of domestic and industrial origins is of particular concern (Fuhrimann et al., 2015; WHO, 2015). It follows that in urban centres of low- and middle-income countries (LMICs), characterised by the lack of improved sanitation, high prevalence and outbreaks of gastrointestinal diseases caused by bacteria, viruses, intestinal protozoa or helminths are common (Matthys et al., 2007; Pham-Duc et al., 2014). However, there is a paucity of disease burden estimates caused by these pathogenic organisms in LMICs (Labite et al., 2010; Katukiza et al., 2013; Machdar et al., 2013).

Exposure to urban wastewater is multifaceted (Stenström et al., 2011; Keraita and Dávila, 2015). Direct exposure occurs through accidental ingestion, inhalation or dermal contact in different

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contexts: (i) during working procedures (e.g. while emptying on-site sanitation facilities, managing wastewater treatment processes or reusing wastewater for irrigation purposes); (ii) while using wastewater for domestic activities (e.g. for cleaning dishes or washing clothes); (iii) during flooding events caused by heavy rains (Cissé, 2013); and (iv) due to recreational activities (e.g. swimming or bathing in lakes or rivers fed by wastewater) (Ferrer et al., 2012; Katukiza et al., 2013; Yapo et al., 2013). Indirect exposure occurs through consumption of contaminated drinking water or wastewater-fed crops and fish (Machdar et al., 2013; Mok and Hamilton, 2014). Reducing exposures to wastewater is therefore a critical inter-sectoral responsibility for protecting public health (Amoah et al., 2011; Keraita and Dávila, 2015). Guidelines published by the World Health Organization (WHO) propose control measures to safely manage and reuse wastewater, excreta and greywater, and to protect recreational and drinking water systems (WHO, 2003, 2006, 2011a). These guidelines are built around the concept of health-based targets that are grounded on well-defined health metrics (e.g. disability-adjusted life years (DALYs)) and a level of tolerable health burden (Mara et al., 2010). Even though this health-based target was recently revised, allowing for a tolerable additional disease burden of 0.0001 DALYs per person per year (pppy), it is still out of reach in many LMICs (Ensink and van der Hoek, 2009; Mara et al., 2010; WHO, 2015).

Disease burden of pathogenic organisms can be estimated by quantitative microbial risk assessment (QMRA) (Haas et al., 2014; Ichida et al., 2015). QMRA commonly follows four working steps: (i) hazard identification; (ii) exposure assessment; (iii) dose-response assessment; and (vi) risk characterisation (Haas et al., 2014). For water-borne hazards, QMRA is widely used in industrialised countries to estimate health risks for drinking water supply systems (Hunter et al., 2000; WHO, 2011a), flood water events (de Man et al., 2014), wastewater management and reuse (Westrell et al., 2004; Ashbolt et al., 2006), storm water discharge (McBride et al., 2013) or recreational water (Soller et al., 2015). It is also widely used for food-borne hazards, based on principles and guidelines defined by Codex Alimentarius (Anonymous, 1995; Havelaar et al., 2008). In LMIC settings, QMRA is becoming increasingly popular and has been successfully applied for the identification of effective control measures for wastewater reuse in urban agriculture systems in Accra and Bangkok (Seidu et al., 2008; Ferrer et al., 2012; Barker et al., 2014) and for risk profiling along drainage channels in Abidjan and Kampala (Katukiza et al., 2013; Yapo et al., 2013). QMRA has also been used to guide cost-effective interventions for drinking water supply systems in Accra and Kampala (Howard et al., 2006; Machdar et al., 2013). It must be noted, however, that these QMRAs suffer from a lack of data on source contamination with pathogens, setting-specific dose-response relationships and validation of the estimated risks with epidemiological data (WHO, 2006; Barker et al., 2014).

To fill some of the aforementioned gaps, this paper presents a QMRA case study for Kampala, the capital of Uganda. Of note, Kampala has undergone rapid population growth and there are large volumes of wastewater in face of insufficiently equipped sanitary infrastructures (Fuhrimann et al., 2015). Microbial and chemical contamination has increased over the past two decades along the major wastewater system (Kansiime and Nalubega, 1999; Kayima et al., 2008; Fuhrimann et al., 2015). For example, concentrations of *Escherichia coli* in wastewater samples are exceeding WHO thresholds of 10^3–10^4 colony forming units (CFU) *E. coli*/100 mL by magnitude of at least 10 (Fuhrimann et al., 2015). Hence, these waters should not be reused without considering additional control measures (WHO, 2006). The mean concentration of *Ascaris lumbricoides* eggs in wastewater and soil samples in slum community areas were above WHO safety standards of ≤1 egg/L (WHO, 2006; Fuhrimann et al., 2015). Using a QMRA approach, the goal of the present study was to estimate the disease burden resulting from exposure to water-borne pathogens causing gastroenteritis along the major wastewater system in Kampala. By comparing the model estimates with findings from epidemiological surveys, advantages and limitations of the QMRA methodology are discussed.

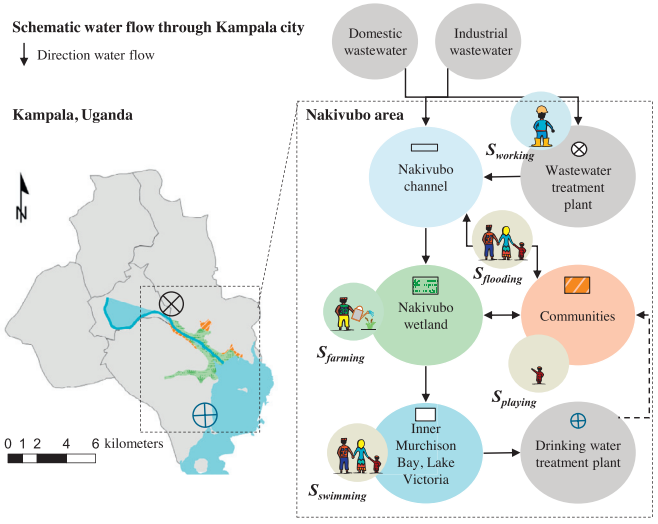

Fig. 1. Schematic flow of Kampala's main wastewater system along the Nakivubo channel, Nakivubo wetland and Lake Victoria with indication of the five exposure scenarios ($S_{flooding}$, $S_{working}$, $S_{farming}$, $S_{playing}$ and $S_{swimming}$).

2. Materials and methods

2.1. Study area

Detailed information and a short video introducing the study area and the sampling scheme have been published elsewhere (Fuhrimann et al., 2014). In brief, Kampala is located at latitude 0° 18′ 49.18″ N and longitude 32° 36′ 43.86″ E at an altitude of 1140 m above the mean sea level. The study area includes the Nakivubo channel in Kampala city (Fig. 1), which is an open storm water channel transporting most of the city's wastewater from the central division (approximately 13,928 m^3/day), comprised of wastewater from households (23%) and industries (77%). Further, the channel receives partially treated effluent from the Bugolobi Sewage Treatment Works (BSTW) (up to 12,000 m^3/day) (Beller Consult et al., 2004). Downstream of the treatment plant, the wastewater enters into the Nakivubo wetland, where it is reused for urban agriculture (main crops: sugar cane, yams and maize). Alongside the Nakivubo wetland, there are informal slum communities prone to flooding events (Fuhrimann et al., 2016). The water is finally discharged into the Inner Murchison Bay in Lake Victoria, a popular recreational area for Kampala's inhabitants, especially along its shores. In addition, only 4 km away from the discharge point, the lake water is pumped and treated to supply Kampala with drinking water (Howard et al., 2006).

2.2. Hazard identification

The hazards considered for the QMRA are seven pathogenic organisms, for which the incidence and disease burden of gastroenteritis due to exposure to wastewater are estimated: two viruses (norovirus and rotavirus), three bacteria (*Campylobacter* spp., pathogenic *Salmonella* spp. and *E. coli*), one intestinal protozoon (*Cryptosporidium* spp.) and one soil-transmitted helminth species (*A. lumbricoides*). All of these pathogens are characterised by the faecal-oral transmission route, can persist for weeks or

months in the environment and are difficult to inactivate with conventional wastewater treatment processes (WHO, 2006; Machdar et al., 2013; Fuhrimann et al., 2015).

Hazard selection was motivated by findings from an environmental assessment and a cross-sectional survey conducted in the study area between October and December 2013 during the short rainy season (Fuhrimann et al., 2015, 2016), along with previous studies about major pathogens giving rise to gastroenteritis in Uganda and elsewhere in the world (Becker et al., 2013; Katukiza et al., 2013; Barker et al., 2014; Gibney et al., 2014). Our selection is further justified on the following grounds:

- Rotavirus is one of the leading causes of childhood diarrhoea, responsible for about 7.3% of deaths among children below the age of 5 years in Uganda and is considered to account for most of the disease burden in slums in Kampala (Katukiza et al., 2013; Sigei et al., 2015).
- Norovirus is the major cause of diarrhoeal disease in adults and its secondary attack rate is known to be high causing epidemic situations, especially in densely populated slum areas (Teunis et al., 2008; Katukiza et al., 2013).
- *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* bacteria are part of the normal gastrointestinal microflora of warm-blooded animals and humans, whilst enterohemorrhagic *E. coli* (EHEC) is considered pathogenic, with the serotype *E. coli* O157:H7 responsible for the largest public health impact (Okeke, 2009; Hynds et al., 2014).
- *Salmonella* spp. have more than 2000 sero-groups, with only a few being of concern for human health (*S. typhi* and *S. paratyphi* A, B and C, and the enteric salmonella strains) (Kariuki et al., 2015).
- *Cryptosporidium* spp. is a zoonotic intestinal protozoon that can result in severe health implications in children and immunocompromised individuals e.g. for HIV-positive people. As the HIV prevalence in Uganda is estimated to be 7.4% – the 10th highest in the world –, *Cryptosporidium* spp. are likely to be of higher public health relevance than, for example, other intestinal protozoa such as *Giardia intestinalis* and *Entamoeba histolytica* (Kaijuka et al., 2011).
- Helminth infections are endemic in the Great Lake region (Karagiannis-Voules et al., 2015; Lai et al., 2015). Prevalence rates for hookworm, *Trichuris trichiura, Schistosoma mansoni* and *A. lumbricoides* in urban farmers in the Nakivubo area were found at 28%, 26%, 23% and 18%, respectively (Fuhrimann et al., 2015). For the current QMRA, the commonly used reference organism *A. lumbricoides* is considered as its eggs are known to persist in the environment longer than any of the other helminth species (Stott et al., 2003).

2.3. Exposure assessment

The exposure scenarios for the QMRA are based on information derived from a survey of 915 people in the Nakivubo area. The findings of this survey have been reported elsewhere (Fuhrimann et al., 2015). Overall, the QMRA only included accidental ingestion of contaminated water and the following exposure pathways were excluded based on the given context: (i) ingestion of contaminated soil, dermal contact, inhalation and drinking of potentially contaminated water (due to lack of data); (ii) consumption of contaminated food crops (not in direct contact with wastewater (sugar cane and maize) or sufficiently cooked (yams)); and (iii) exposure to contaminated water used for bathing or washing clothes (uncommon local practice).

Five exposure scenarios in four study areas (Nakivubo channel, Nakivubo wetland, community areas and shores of Lake Victoria) were developed and assumptions about exposure groups, number of people exposed, exposure frequency and volume of ingested water are made (Fig. 2).

- **Scenario 1 ($S_{flooding}$):** Slum dwellers (all age groups) living in close proximity to the Nakivubo wetland are located on low altitude and, hence, were prone to flooding events. Almost half (47%) of the people living in these communities reported having been exposed to flooding events in the previous year (i.e. 5640 out of 12,000 people) (Fuhrimann et al., 2016). According to Lwasa and colleagues (2010), six flooding events may occur during the two rainy seasons (March to May and September to November) in one year. During a flooding event, ingestion of water due to unintentional immersion is assumed to be between 10 and 30 mL (Katukiza et al., 2013).
- **Scenario 2 ($S_{working}$):** There are 231 registered sanitation workers. 90 workers are employed by the National Water and Sewerage Corporation (NWSC) and responsible for the maintenance of the drainage system and the operation of the BSTW. Those working for the Pit Emptier Association (PEA) ($n = 141$), are responsible for emptying of on-site toilet facilities and transfer of the faecal sludge to BSTW (Fuhrimann et al., 2016). Their working practices expose workers to wastewater and faecal sludge (Stenström et al., 2011). On average, workers report 312 days on duty per year, with 70% of the workers regularly wearing boots and gloves. An accidental ingestion between 1 and 5 mL per working day is assumed (10-times less compared to workers without protective equipment) (WHO, 2006; Labite et al., 2010; Mara and Bos, 2010).
- **Scenario 3 ($S_{farming}$):** The farming areas in the Nakivubo wetland are frequently flooded with polluted water from Nakivubo channel, combined with effluent from BSTW, and the area bordering Lake Victoria is defined as floating wetland (Kansiime and Nalubega, 1999). Thus, the likelihood of accidental ingestion of wastewater is considerable. Overall, approximately 650 urban farmers (>15 years of age) reported working within the Nakivubo wetland. On average, farmers reported to work 297 days per year and only 3% of them regularly wear boots and gloves (Fuhrimann et al., 2016). An accidental ingestion between 10 and 50 mL per working day is assumed (WHO, 2006; Labite et al., 2010; Mara and Bos, 2010).
- **Scenario 4 ($S_{playing}$):** Children living in slum communities are at an elevated risk of daily accidental ingestion of water (Katukiza et al., 2010). Due to flooding events and poor sanitation infrastructures, slum environments are constantly contaminated (Fuhrimann et al., 2016) and children aged <15 years are considered at risk when playing (49.4%, 5,880 children out of 12,000 people) (UBOS, 2013). Exposure is assumed to be daily (365 days per year) with an accidental ingestion rate between 1 and 5 mL per day (Labite et al., 2010; Katukiza et al., 2013).
- **Scenario 5 ($S_{swimming}$):** Several studies found adverse health outcomes associated with exposure to contaminated recreational water (WHO, 2003; Schets et al., 2011; Yapo et al., 2013). In Kampala, swimming at the local beaches along the Inner Murchison Bay (e.g. Miami Beach, Ggaba Beach, KK Beach) is popular (Beller Consult et al., 2004). However, in our previous study, only three out of 915 individuals interviewed (0.32%) reported to have swum in Lake Victoria in the year preceding the survey (Fuhrimann et al., 2016). This is likely to be an underestimate as only people from lower socioeconomic strata were included in the survey and may not be able to access the private beaches. Still, when extrapolating this to the 1.8 million inhabitants of Kampala, 5760 people can be estimated to be swimming in the Inner Murchison Bay of Lake Victoria. It is assumed

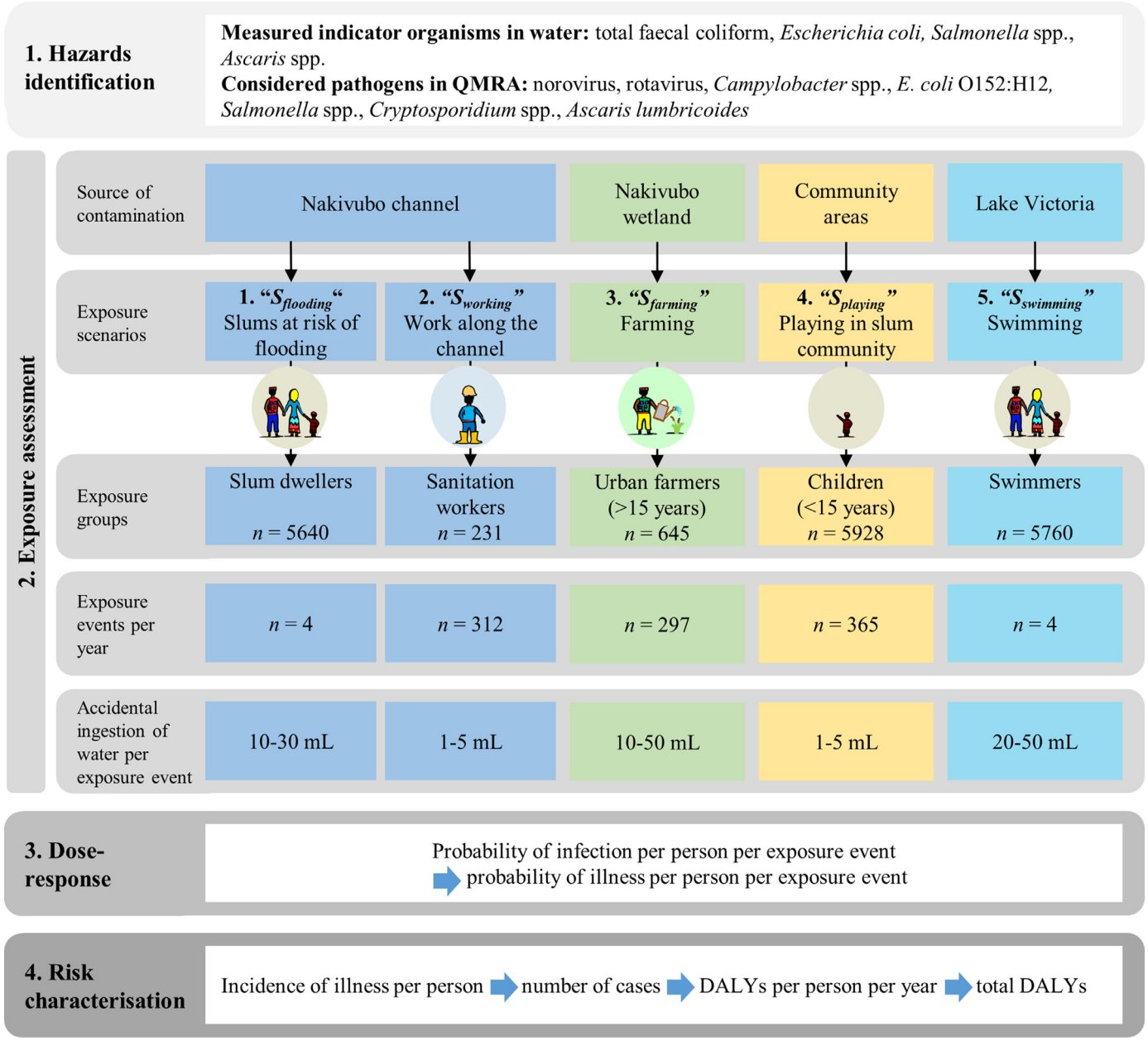

Fig. 2. Exposure scenarios ($S_{flooding}$, $S_{working}$, $S_{farming}$, $S_{playing}$ and $S_{swimming}$) considered in the quantitative microbial risk assessment (QMRA) to estimate the burden of *Campylobacter* spp., *Escherichia coli* O157:H7, *Salmonella* spp., norovirus, rotavirus, *Cryptosporidium*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

these people swim six times per year in the Lake, ingesting 20 to 50 mL per swimming event (WHO, 2003; Schets et al., 2011; Fuhrimann et al., 2016).

2.4. Measurements of pathogenic organisms along the wastewater system

Between October and December 2013, wastewater samples were collected at 23 sentinel sites along the Nakivubo channel (five points) and wetland (12 points), community areas bordering the Nakivubo wetland (two points) and within the Inner Murchison Bay in Lake Victoria (four points). The samples were tested for *E. coli*, thermotolerant coliforms (TTC), *Salmonella* spp. and helminth eggs. Details of the methodology and sampling strategy, including measurements of heavy metals and physicochemical parameters, have been published elsewhere (Fuhrimann et al., 2015). According to guidance documents put forth by WHO, the ratio between measured *E. coli* and the pathogens (p_{path}) can be simplified and therefore assumed to vary between 10^{-6}–10^{-5} (rotavirus, norovirus and *Campylobacter* spp.) and 10^{-7}–10^{-6} (*Cryptosporidium* spp.) (Haas et al., 1999). The ratio between pathogenic and non-pathogenic strains of *E. coli* (p_{path}) was set to vary between 7.6×10^{-4} and 1×10^{-2} (Shere et al., 2002; Soller et al., 2010; Hynds et al., 2014). In the absence of data, the same ratio was assumed for *Salmonella*. For *Ascaris* spp. it was assumed that each egg detected represents *A. lumbricoides* ($p_{path} = 1$, not considering the occurrence of other species such as *A. suum*) (Mara and Sleigh, 2010).

2.5. QMRA structure, implementation and analysis

2.5.1. QMRA structure

In most points, our QMRA approach follows the descriptions of the WHO 2006 guidelines and Karavarsamis and Hamilton (WHO, 2006; Karavarsamis and Hamilton, 2010; Mara et al., 2010).

However, we purposely do not adopt the entire approach, because we do not aim to study the overall infection risk but the disease burden, which needs estimates of the number of cases for each of the hazards separately. Hence, in addition, three adjustments were made. First, we used quantitative data on *E. coli, Salmonella* spp. and *Ascaris* spp. eggs obtained in the research area and fitted them to log-normal distribution, while prevalence estimates were used for *Ascaris* eggs (Fuhrimann et al., 2015). Second, our QMRA allows people to get ill from more than one hazard at the same time and the mean risk of illness was calculated over the duration of one year for each person, while assuming that each individual can become infected with each exposure event (without considering immunity) (Haas et al., 2014). Third, the corresponding disease burden for each of the seven selected pathogens was calculated according to published probability estimates for mild, moderate, severe and fatal gastroenteritis (Havelaar et al., 2000; Brooker, 2010; Katukiza et al., 2013; Gibney et al., 2014). Note that probability estimates for the severity grade were taken from other countries than Uganda, as no local estimates exist. Burden estimates for mild, moderate and severe diarrhoea episodes were taken from the Global Burden of Disease Study 2010 (Salomon et al., 2012). Mortality was calculated according to the average life expectancy at birth in Uganda of 54.20 years from 2008 (World Bank, 2016). Finally, sequelae such as Guillain–Barré syndrome, reactive arthritis or irritable bowel syndrome are not considered in the model.

2.5.2. QMRA implementation and analysis

As summarised in Table 1, spatial and temporal variability of the number of CFU of *E. coli, Salmonella* spp. and number of eggs of *Ascaris* spp. were measured from October to December 2013 during the short rainy season at 23 sampling points over the four study areas. For *E. coli* and *Salmonella* spp., we fitted normal distributions to the log-transformed enumeration data on concentration in the water (C_{water}), using a maximum likelihood estimation (MLE) method, 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 was not possible as only four out of 168 (excluding Lake Victoria) samples were positive. Hence, with a value of 0.024, a positive count is expected, between 1 and 100 eggs/L, which is included with uniform distribution on a log-scale (Fuhrimann et al., 2015). 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:

$$d = C_{water} \times \ p_{path} \times \ V \tag{1}$$

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 ($d \sim$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 $P_I(d)$ (Eqs. (1)–(3)). 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 and associated $P_{ill}(d)$ of one person in a year. Based on this, the expected frequency of illness for this person per year (which, in our approach, can be more than one) can be calculated as the sum of the n values of $P_{ill}(d)$ obtained. Model outputs are presented as number of cases per year, DALYs pppy and total DALYs per year (see Eqs. (6), (9) and (10)).

2.6. Dose-response models

Well-established dose-response models for the various pathogens were used 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, the simplified Beta-Poisson dose-response models for rotavirus, *Campylobacter* spp., *E. coli* O157:H7, pathogenic *Salmonella* spp. and *A. lumbricoides* were employed (Teunis and Havelaar, 2000; McBride et al., 2013; Haas et al., 2014), as defined as

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

with a median infectious dose defined as

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

For norovirus, a hypergeometric function is presented by Teunis et al. (2008), which is fit to run with the @Risk software, version 6 (Palisade Corporation; Newfield, NY, USA) and to include the uncertainty about the dose-response. We used an approximation for the mean probability of infection (Haas, 2002) of the Beta-Poisson dose-response model:

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

where $\Gamma(.)$ represents Eulers gamma function. For *Cryptosporidium* spp., an exponential model was used (Westrell et al., 2004; de Man et al., 2014; McBride et al., 2013):

$$P_I(d) = 1 - (1-r)^d \tag{5}$$

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 gastroenteritis cases ($P_{ill}(d)$), we used for each pathogen a constant value (λ) (i.e. illness to infection ratio):

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

Table 1 provides the parameter values used in the QMRA for each pathogen. Moreover, for $P_{ill}(d)$ we use the probability of a symptomatic gastroenteritis for each of the seven pathogens (or hazards) h, $P_{ill,h}(d_i)$, which is a function of the ingested dose d_i at exposure event i (Haas et al., 2014).

2.7. Risk characterisation

2.7.1. Incidence: the number of cases per year

Our model assumed that each exposure event i is independent and that there is no immunity after a previous infection (no dose-response available for the context of LMICs and, hence, it is not possible to include immunity status of exposed population groups

Table 1
QMRA model parameter, distributions and assumptions.

Description	Units	Distribution and/or values	Reference(s)
(C_{water}) Concentrations: water Nakivubo channel			Fuhrimann et al., 2015
Escherichia coli	$\log_{10}$ (CFU/100 mL)	Normal(6.0;1.1)[a]; prevalence = 1	
Salmonella spp.	$\log_{10}$ (CFU/100 mL)	Normal(2.7;0.8)[a]; prevalence = 1	
Ascaris spp.	$\log_{10}$ Eggs/1 L	Uniform(0;2)[b]; prevalence = 0.024	
(C_{water}) Concentrations: water Nakivubo wetland			
E. coli	$\log_{10}$ (CFU/100 mL)	Normal(5.0;1.5)[a]; prevalence = 1	
Salmonella spp.	$\log_{10}$ (CFU/100 mL)	Normal(2.1;1.3)[a]; prevalence = 0.95	
Ascaris spp.	$\log_{10}$ Eggs/1 L	Uniform(0;2)[b]; prevalence = 0.024	
(C_{water}) Concentrations: water community areas			
E. coli	$\log_{10}$ (CFU/100 mL)	Normal(5.9;1.4)[a]; prevalence = 1	
Salmonella spp.	$\log_{10}$ (CFU/100 mL)	Normal(2.1;1.3)[a]; prevalence = 1	
Ascaris spp.	$\log_{10}$ Eggs/1 L	Uniform(0;2)[b]; prevalence = 0.024	
(C_{water}) Concentrations: water Lake Victoria			
E. coli	$\log_{10}$ (CFU/100 mL)	Normal(1.8;3.0)[a]; prevalence = 0.69	
Salmonella spp.	$\log_{10}$ (CFU/100 mL)	Normal(0.6;2.0)[a]; prevalence = 0.50	
Ascaris spp.	$\log_{10}$ Eggs/1 L	Uniform(0;2)[b]; prevalence = 0.024	
(p_{path}) Ratio between indicator and pathogenic organisms			
A. lumbricoides to *Ascaris* spp.		Point estimate: $p_{path} = 1$	Mara et al., 2010
Campylobacter spp. to *E. coli*		PERT(0.1;0.55;1)[c] per 10^5 *E. coli*	WHO, 2006
Cryptosporidium spp. to *E. coli*		PERT(0.01;0.055;0.1)[c] per 10^5 *E. coli*	WHO, 2006
Pathogenic E. coli: O157:H7 to *E. coli*		Uniform (7.6×10^{-4};1×10^{-2})[b]	Shere et al., 2002; Soller et al., 2010; Hynds et al., 2014
Norovirus to *E. coli*		PERT(0.1;0.55;1)[c] per 10^5 *E. coli*	WHO, 2006
Rotavirus to *E. coli*		PERT(0.1;0.55;1)[c] per 10^5 *E. coli*	Katukiza et al., 2013
Pathogenic *Salmonella* to *Salmonella* spp.		Uniform (7.6×10^{-4};1×10^{-2})[b]	Shere et al., 2002; Soller et al., 2010; Hynds et al., 2014
(V) Volume ingested per exposure event for each scenario			
$S_{flooding}$	mL	PERT(10;20;30)[c]	Katukiza et al., 2013
$S_{working}$	mL	PERT(1;3;5)[c]	WHO, 2006; Labite et al., 2010
$S_{farming}$	mL	PERT(10;35;50)[c]	WHO, 2006; Labite et al., 2010
$S_{playing}$	mL	PERT(1;3;5)[c]	Katukiza et al., 2013
$S_{swimming}$	mL	PERT(20;35;50)[c]	Schets et al., 2011; Yapo et al., 2013
Dose-response models			
A. lumbricoides		Point estimate: $\alpha = 0.0104$; $N_{50} = 859$	Mara et al., 2010
Campylobacter spp.		Point estimate: $\alpha = 0.145$; $N_{50} = 896$	Medema et al., 1996
Cryptosporidium spp.		Point estimate: $r = 0.0042$	Haas et al., 1999
E. coli O157:H7		Point estimate: $\alpha = 0.49$; $N_{50} = 596{,}000$	Teunis et al., 2008
Norovirus		Point estimate: $\alpha = 0.04$; $\beta = 0.055$;	Teunis et al., 2008
Rotavirus		Point estimate: $\alpha = 0.253$; $N_{50} = 6$	Teunis and Havelaar, 2000
Pathogenic *Salmonella* spp.		Point estimate: $\alpha = 0.3126$; $N_{50} = 23{,}600$	Haas et al., 1999
(λ) Illness to infection ratio			
A. lumbricoides		Point estimate: 0.39	Mara et al., 2010
Campylobacter jejuni		Point estimate: 0.3	Machdar et al., 2013
Cryptosporidium		Point estimate: 0.79	Machdar et al., 2013
Pathogenic E. coli		Point estimate: 0.35	Machdar et al., 2013
Norovirus		Point estimate: eta = 0.00255; $r = 0.086$	Teunis et al., 2008
Rotavirus		Point estimate: 0.5	Barker et al., 2014
Pathogenic *Salmonella* spp.		Point estimate: 1	McBride et al., 2013
(n) number of exposure events per year			Fuhrimann et al., 2016; UBOS, 2013
$S_{flooding}$		Point estimate: 6	
$S_{working}$		Point estimate: 312	
$S_{farming}$		Point estimate: 297	
$S_{playing}$		Point estimate: 365	
$S_{swimming}$		Point estimate: 6	
(Pop_E) population at risk per exposure scenario			Fuhrimann et al., 2016
$S_{flooding}$	People at risk of flooding	Point estimate: 5640	
$S_{working}$	Workers	Point estimate: 231	
$S_{farming}$	Urban farmers	Point estimate: 645	
$S_{playing}$	Children in slum communities	Point estimate: 5928	
$S_{swimming}$	People swimming in Lake Victoria	Point estimate: 5760	
($DALY_h$) disease burden per pathogenic organisms (disability-adjusted life years (DALYs) calculation is indicated in Table 2)			
A. lumbricoides	DALYs/case	Point estimate: 0.0029	
Campylobacter spp.	DALYs/case	Point estimate: 0.0053	
Cryptosporidium spp.	DALYs/case	Point estimate: 0.0022	
Pathogenic *E. coli*	DALYs/case	Point estimate: 0.0013	
Norovirus	DALYs/case	Point estimate: 0.0008	
Rotavirus	DALYs/case	Point estimate: 0.0032	
Pathogenic *Salmonella* spp.	DALYs/case	Point estimate: 0.0719	

[a] Normal distribution (mean; standard deviation).
[b] Uniform distribution (min; max).
[c] Project evaluation and review techniques (PERT) (min; most likely; max).

Table 2
Disease burden due to gastroenteritis expressed in disability-adjusted life years (DALYs) calculated by means of severity (mild, moderate, severe and fatality), probability, and duration of the respective severity grade per pathogen.

Gastroenteritis		Severity weights					Reference(s)
		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	54.20[a]		
	DALYs	3.24×10^{-4}	9.56×10^{-5}	3.33×10^{-5}	4.23×10^{-4}	8.75×10^{-4}	
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	54.20[a]		
	DALYs	6.94×10^{-4}	4.01×10^{-4}	2.96×10^{-4}	1.83×10^{-3}	3.22×10^{-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
	Duration (days)	3.50	9.70	14.40	-		Gibney et al., 2014
	Duration (years)	0.01	0.03	0.04	54.20[a]		
	DALYs	4.70×10^{-4}	9.72×10^{-4}	1.77×10^{-4}	3.64×10^{-3}	5.26×10^{-3}	
Pathogenic *Salmonella* 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	54.20[a]		
	DALYs	8.61×10^{-5}	2.18×10^{-3}	1.27×10^{-3}	6.85×10^{-2}	7.20×10^{-2}	
Pathogenic *Escherichia coli*	Probability	0.94	0.06	0.09	2.00×10^{-4}		Katukiza et al., 2013
	Duration (days)	5.60	10.70	16.20	1.00		
	Duration (years)	0.02	0.03	0.04	54.20[a]		
	DALYs	8.80×10^{-4}	3.55×10^{-4}	1.12×10^{-3}	1.08×10^{-2}	1.13×10^{-2}	
Ascaris lumbricoides	Probability	0.95	0.05	-	-		Brooker, 2010
	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}	

[a] Average life expectancy at birth in Uganda from 2008 (World Bank, 2016).

in this model). For an average of n_h exposures to the hazard per person per year, with population size Pop_E, the expected number of cases in the population is:

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

The incidence estimate for pathogen h is:

$$Inc_h = \frac{Cases_h}{Pop_E} \tag{8}$$

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

$$Inc_{comb} = \sum_{all\ h} \frac{Cases_h}{Pop_E} \tag{9}$$

2.7.2. Estimation of disease burden

The disease burden was expressed by the DALY metric. This metric combines morbidity (years lived with disability) and premature death (years of life lost) (Murray et al., 2012). For each pathogen h, DALY per case of gastrointestinal illness ($DALY_h$) was estimated 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 a case of gastroenteritis, relative frequency of the symptom (f_j), duration of the developed symptom in years (D_j) and the respective severity factor (Sj) (Table 2) (Salomon et al., 2012):

$$\mathrm{DALY}_h = \sum_j \left(f_j \times D_j \times S_j\right) \tag{10}$$

The total disease burden ($Total_{\mathrm{DALY}s,h}$) per hazard was the product of cases ($Cases_h$) and DALYs per pathogen:

$$Total_{\mathrm{DALY}s,h} = Cases_h \times \mathrm{DALY}_h \tag{11}$$

2.8. Sensitivity analysis to detect uncertainty and effect of potential interventions

To explore the uncertainty around the model outputs in DALYs, a nominal range sensitivity analysis (NRSA) was done. The NRSA was employed for scenario $S_{playing}$ only to exemplify the impact of small changes in some of the model parameters used. Selected individual inputs were varied over a certain range, while holding all other inputs at their nominal values (Table 3). The following five parameter groups were investigated to obtain information about their uncertainty and effect of a potential intervention: (i) (V) volume ingested per exposure event were based on assumptions and, hence, values were multiplied by 0.1 and 10; (ii) (p_{path}) ratio between indicator and pathogenic organisms vary considerably between different contexts and, hence, values were multiplied by 0.1 and 10; (iii) (C_{water}) water contamination in community areas and the potential effect of treatment while varying the concentration with 1 log; (iv) (n) number of exposure events per year vary according to implemented health education programmes and, hence, we simulated a reduction by half (153 events) and to one event per year; and (v) (Pop_E) population at risk per exposure scenario may also vary according to the exposure event, we multiplied the population by 0.1 and 10.

2.9. 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) and the Uganda National Council for Science and Technology (UNCST; Kampala, Uganda; reference no. HS 1487). Ethical approval was obtained from the ethics committee in Basel (EKBB; reference no. 137/13) and the Higher Degrees Research and Ethics Committee

Table 3
Sensitivity analysis of input parameters of the model indicated for scenario $S_{playing}$.

Scenarios		Description	Units	Distribution	Estimates Upper	Lower
Uncertainty (*V*)						
Volume ingested per exposure event	*1*		mL	PERT(1;3;5)[a]	10;30;50	0.1;0.3;0.5
(p_{path}) Ratio between indicator and pathogenic organisms	*2.1*	Norovirus to *E. coli*		PERT(0.1;0.55;1)[a] per 10^5 *E. coli*	10;55;100	0.01;0.055;0.1
	2.2	Rotavirus to *E. coli*		PERT(0.1;0.55;1)[a] per 10^5 *E. coli*	10;55;100	0.01;0.055;0.1
	2.2	*Campylobacter* spp. to *E. coli*		PERT(0.1;0.55;1)[a] per 10^5 *E. coli*	1;5.5;10	0.01;0.055;0.1
	2.3	Pathogenic *E. coli* to *E. coli*		Uniform(7.6×10^{-4};1×10^{-2})[b]	$0.1–7.6 \times 10^{-3}$	$1 \times 10^{-3}–7.6 \times 10^{-5}$
	2.4	Pathogenic *Salmonella* to *Salmonella* spp.		Uniform(7.6×10^{-4};1×10^{-2})[b]	$1–7.6 \times 10^{-2}$	$1 \times 10^{-3}–7.6 \times 10^{-5}$
	2.5	*Cryptosporidium* spp. to *E. coli*		PERT(0.01;0.055;0.1)[a] per 10^5 *E. coli*	0.1;0.5.5;1	0.001;0.0055;0.01
Interventions						
(C_{water}) Water contamination in community areas	*3.1*	*Escherichia coli*	$\log_{10}$ (CFU/100 mL)	Normal(5.9;1.4)[c]	6.9	4.9
	3.2	*Salmonella* spp.	$\log_{10}$ (CFU/100 mL)	Normal(2.1;1.3)[c]	3.1	2.1
	3.3	*Ascaris* spp.	$\log_{10}$ eggs/1 L	Uniform(0;2)[b]	0–3	0–1
(*n*) Number of exposure events per year	*4*	Children in slum communities	Events	Point estimate: 365	1	153
(Pop_E) Population at risk per exposure scenario	*5*	Number of children	Children	Point estimate: 5928	592	59,280

[a] Project evaluation and review techniques (PERT) (min; most likely; max).
[b] Uniform distribution (min; max).
[c] Normal distribution (mean; standard deviation).

of Makerere University, School of Public Health (Kampala, Uganda; reference no. IRBOOO11353). This study is registered with the clinical trial registry ISRCTN (identifier: ISRCTN13601686).

3. Results

3.1. Incidence of gastroenteritis per year

The combined estimated incidence (Inc_{comb}) was highest for urban farmers ($S_{farming}$), children living in slum communities ($S_{playing}$) and sanitation workers ($S_{working}$) who suffer from 10.9, 8.3 and 4.3 gastroenteritis episodes per person per year (mean values; Fig. 3 and Table 4). The lowest risk was estimated for people swimming in Lake Victoria ($S_{swimming}$) who suffer from 0.18 gastroenteritis episodes per year. With regard to the individual pathogens, the risk of gastrointestinal infection was highest for children ($S_{playing}$) and urban farmers ($S_{playing}$) for rotavirus (4.4 and 3.9 episodes per year, respectively) and *E. coli* (2.7 and 1.7 episode per year, respectively). Considerably lower incidences were estimated for the same scenarios for *A. lumbricoides* (0.062 and 0.001 episode per year, respectively) and norovirus (between 0.46 and 0.34 episode per year, respectively).

3.2. Number of gastroenteritis cases per year

Among the overall 18,204 exposed people in the Nakivubo area, 59,493 cases of gastroenteritis were estimated due to any of the seven pathogens, five scenarios and over the duration of one year (Fig. 3 and Table 4). Gastrointestinal infection due to rotavirus, *E. coli* and *Cryptosporidium* contributed most to the total cases (46%, 21% and 17%, respectively), followed by *Campylobacter* spp. (12%) and norovirus (4%). Together, 82% of all cases were concentrated in the 5,928 children living in slum communities ($S_{playing}$: 48,882 cases) and 650 urban farmers ($S_{farming}$: 7111 cases).

3.3. Total disease burden per year

Across all five scenarios, the model estimated a burden of 304.3 DALYs per year due to exposure to wastewater in the Nakivubo area among 18,204 exposed people, for all seven pathogens together (Fig. 3 and Table 4). The main responsible pathogens were *E. coli*, rotavirus and *Campylobacter*, accounting for 46%, 29% and 12% of DALYs, respectively. Children living in slum communities ($S_{playing}$; $n = 5928$) and urban farmers ($S_{farming}$; $n = 645$) were most vulnerable with burdens of 236.8 and 47.8 DALYs, respectively.

3.4. Disease burden per person per year

Combined DALYs pppy for all scenarios (summed-up for the seven pathogens and all exposed individuals) were far above the revised WHO reference level of 0.0001 DALYs pppy (Fig. 3 and Table 4). The highest impact was estimated for urban farmers in the Nakivubo wetland ($S_{farming}$), children living in slum communities ($S_{playing}$) and workers maintaining sanitation infrastructures ($S_{working}$), with DALYs pppy of 0.074, 0.040 and 0.017, respectively. In terms of different pathogens in $S_{farming}$, *E. coli, Salmonella* spp. and rotavirus had the largest share with 0.031, 0.018 and 0.014 DALYs pppy, respectively.

3.5. Sensitivity analysis

The effect of the sensitivity analysis, stratified for uncertainty and intervention scenarios, is shown in Fig. 3 for total cases of gastroenteritis. Uncertainty analysis revealed the highest change when adapting the volume of water accidentally ingested (−0.69 and 0.58). The pathogen ratio showed highest variation for rotavirus, *Cryptosporidium* and *E. coli*. Intervention strategies to reduce the water contamination with *E. coli* would have an impact of 0.70 and 0.58. Reducing the number of exposure events by half or to one event per year would reduce the number of gastroenteritis episodes by 0.29 and 2.56, respectively. The change of population at risk was found to be proportional to the indicated people exposed.

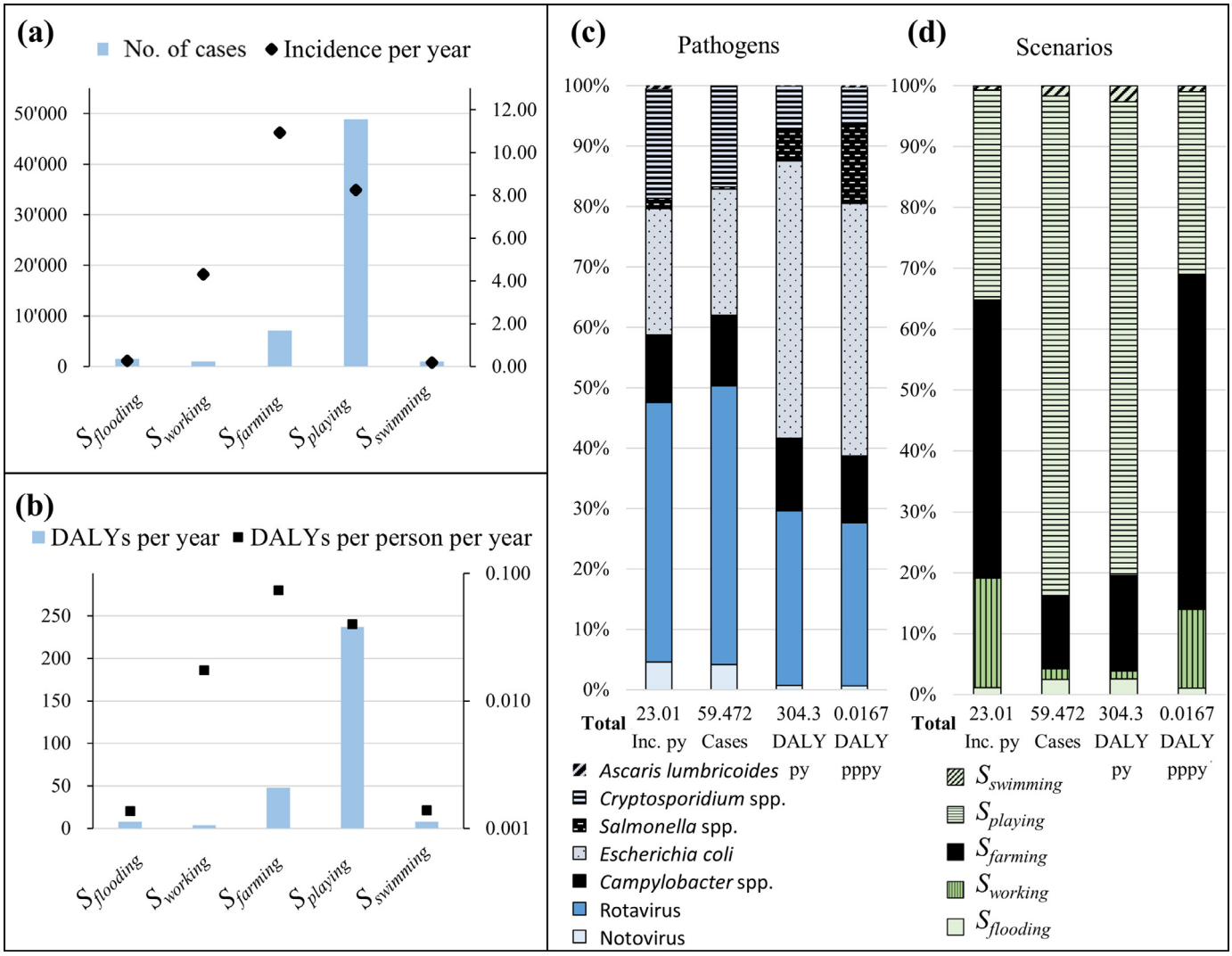

Fig. 3. Estimated gastroenteritis incidence per year (Inc. py), number of cases, disability-adjusted life years (DALYs) per year (py) and per person per year (pppy). (a) and (b) are showing estimates of the respective outcomes per $S_{flooding}$, $S_{working}$, $S_{farming}$, $S_{playing}$ and $S_{swimming}$. (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 Kampala.

4. Discussion

4.1. Estimated burden due to gastroenteritis

Our estimated disease burden of 304.3 DALYs across all 18,204 exposed people per year corresponds to the estimates by the global burden of diseases study for entire Uganda of 0.017 DALYs pppy (612,202 DALYs considering a total population of Uganda of 35.4 million people) (GBD, 2010; UBOS, 2013). Broken down to the individual exposure groups in our model, urban farmers, children in slum communities and sanitation workers experience a 7, 3 and 2 times higher disease burden due to gastroenteritis than the general population in Uganda, respectively. These estimates are still lower than the disease burden estimates made for a typical slum area in Kampala of 10,172 DALYs (15,015 people) (Katukiza et al., 2013) and the 31,979 DALYs for 286,833 people being exposed to the urban wastewater systems in Accra (Labite et al., 2010). This large discrepancy between the QMRA estimates can partly be explained by different pathogens used for the QMRA, applied DALY estimates per pathogens (e.g. we excluded sequelae) and methodological differences (e.g. in the calculation of risk of illness). A common finding of QMRA studies in Africa is that *E. coli* and rotavirus together cause more than half of the disease burden (Katukiza et al., 2013; Machdar et al., 2013). The relatively high model-based estimate for pathogenic *E. coli* is supported by a recent case-control study in Côte d'Ivoire, which found that enterotoxigenic *E. coli* is indeed one of the most prevalent pathogens, being the causative agent in 32% of all participants with persistent diarrhoea (≥2 weeks) (Becker et al., 2015). The importance of rotavirus infection was demonstrated in an investigation at the Mulago Hospital in Kampala, where the rotavirus was detected in 177 out of 390 children aged 3 to 59 months (45.4%) presenting with acute diarrhoea (Nakawesi et al., 2010). Accordingly, the WHO reports that rotavirus is the main diarrhoea-causing agent in this age group, causing 7.3% of all deaths in children aged under 5 years in Uganda (Sigei et al., 2015).

4.2. Estimated incidence of gastroenteritis

Few papers have compared or even validated QMRA estimates with diarrhoea episodes assessed by epidemiological studies (Bouwknegt et al., 2014; Haas et al., 2014). In conjunction with the environmental assessment carried out for the QMRA, we have implemented a cross-sectional epidemiological survey in slum dwellers at risk of flooding events, urban farmers and sanitation workers (Fuhrimann et al., 2016). In this survey the self-reported

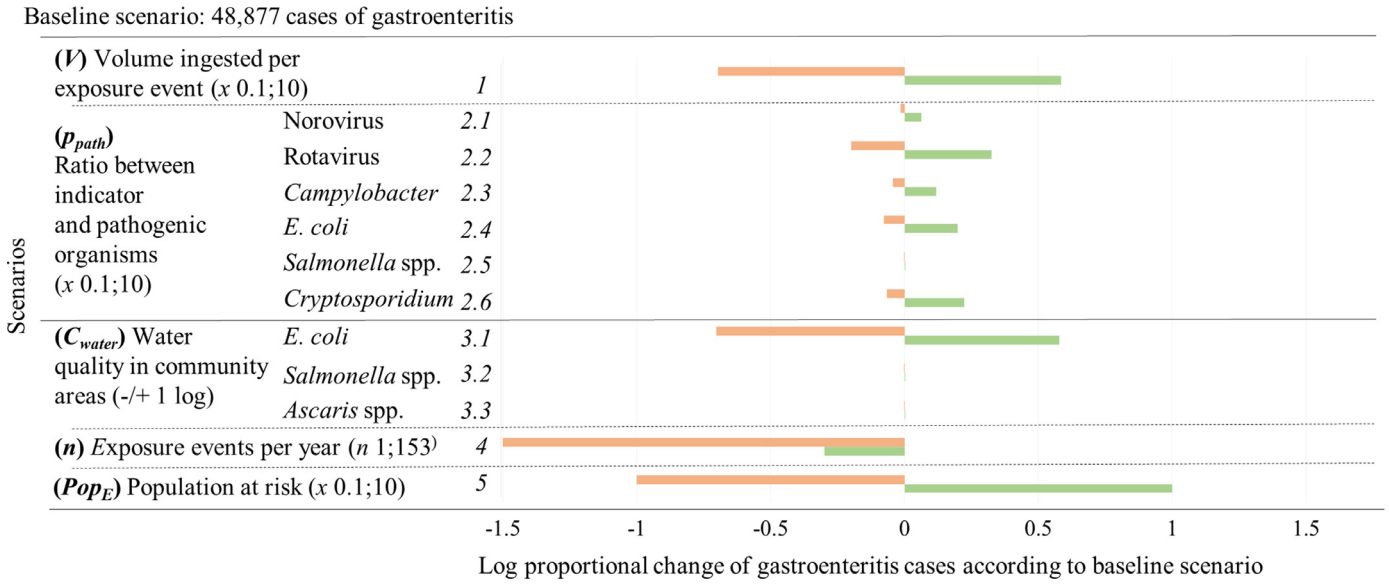

Fig. 4. Sensitivity analysis showing change in log(proportion) of gastroenteritis cases according to the baseline scenario ($S_{playing}$, children in slum communities) and stratified in uncertainty and intervention scenarios. Green line = upper estimates; red line = lower estimates. *indicating change in parameter values (upper; lower estimates). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 4
QMRA estimates for annual incidence of illness, number of cases per year, total DALYs per year, DALYs per person per year across all five exposure scenarios ($S_{flooding}$, $S_{working}$, $S_{farming}$, $S_{playing}$ and $S_{swimming}$) and seven pathogens along the major wastewater system in Kampala.

Exposure scenario (n = exposed population)	$S_{flooding}$ (n = 5640)	$S_{working}$ (n = 231)	$S_{farming}$ (n = 645)	$S_{playing}$ (n = 5928)	$S_{swimming}$ (n = 5760)	Total (n = 18,204)
Incidence of gastroenteritis per year (Inc_h)						
Norovirus	0.010	0.106	0.459	0.342	0.012	0.93
Rotavirus	0.127	1.812	4.402	3.880	0.055	10.28
Campylobacter	0.032	0.425	1.158	0.985	0.018	2.62
E. coli	0.053	0.675	2.697	1.679	0.032	5.14
Salmonella spp.	0.001	0.010	0.251	0.001	0.009	0.27
Cryptosporidium	0.039	0.371	1.893	1.355	0.050	3.71
A. lumbricoides	0.001	0.003	0.062	0.003	0.001	0.07
Total number	0.26	3.31	10.92	8.25	0.18	23.01
No. cases per year ($Cases_h$)						
Norovirus	57	25	299	2′030	70	2′480
Rotavirus	719	419	2′861	23′000	319	27′317
Campylobacter	178	98	753	5′837	101	6′966
E. coli	300	156	1′753	9′955	182	12′345
Salmonella spp.	7	2	163	4	51	227
Cryptosporidium	218	86	1′230	8′035	287	9′856
A. lumbricoides	5	1	40	17	8	71
Total number	1483	996	7099	48,877	1017	59,472
DALYs per year ($Total_{DALYs,h}$)						
Norovirus	0.0	0.0	0.3	1.8	0.1	2
Rotavirus	2.3	1.3	9.2	74.1	1.0	88
Campylobacter	0.9	0.5	4.0	30.7	0.5	37
E. coli	3.4	1.8	19.8	112.5	2.1	139
Salmonella spp.	0.5	0.2	11.7	0.3	3.6	16
Cryptosporidium	0.5	0.2	2.7	17.4	0.6	21
A. lumbricoides	0.0	0.0	0.1	0.1	0.0	0
Combined DALYs	7.7	4.0	47.8	236.8	8.0	304.3
DALYs per person per year ($DALY_{pppy,h}$)						
Norovirus	0.0000	0.0001	0.0004	0.0003	0.0000	0.0001
Rotavirus	0.0004	0.0058	0.0142	0.0125	0.0002	0.0048
Campylobacter	0.0002	0.0022	0.0061	0.0052	0.0001	0.0020
E. coli	0.0006	0.0076	0.0305	0.0190	0.0004	0.0076
Salmonella spp.	0.0001	0.0007	0.0181	0.0000	0.0006	0.0009
Cryptosporidium	0.0001	0.0008	0.0041	0.0029	0.0001	0.0012
A. lumbricoides	0.0000	0.0000	0.0002	0.0000	0.0000	0.0000
Combined DALYs	0.0014	0.0172	0.0741	0.0400	0.0014	0.0167

14-day incidence of diarrhoea episodes ranged from 0.25 in slum dwellers and urban farmers to 0.29 in workers along the sanitation system. When extrapolating this 14-day incidence to 1 year (52 weeks, without considering seasonality), the annual incidence would range between 6.6 and 7.6 episodes pppy. The comparison of the incidence estimate from the cross-sectional survey with the combined incidence of all seven pathogens used for the QMRA reveals that estimates are similar (i.e. 10.9 *versus* 6.6 in urban farmers and 4.3 *versus* 7.6 in sanitation workers, 0.3 *versus* 6.6 in community members). Hence, the estimates might match even more had the QMRA included the level of immunity (reduction in estimates) and additional exposures adding to diarrhoea incidence such as human to human transmission or consumption of contaminated water and food (Machdar et al., 2013; Barker, 2014). Further, when focusing on helminth infections, the QMRA estimated 92 people to be infected with *A. lumbricoides* over the course of a year, with 52 cases occurring in urban farmers (8% of the total number). The incidence estimate is in contrast to findings from our cross-sectional survey, which showed high prevalence in adult urban farmers: *A. lumbricoides:* 18.4%; *T. trichiura:* 26.1%; hookworm: 27.8%; and *S. mansoni* 22.9%, respectively (Fuhrimann et al., 2016). The comparatively low model-based estimates can be explained by the low prevalence and concentration of helminth eggs measured in wastewater samples. Indeed, only four samples were positive for *Ascaris* spp. eggs out of 168 (Fuhrimann et al., 2015). On the other hand, the high prevalence in urban farmers may result from accumulation of worms over time as deworming was reported not to be done on a regular basis (Fuhrimann et al., 2016). Similar tendencies, i.e. higher risk estimates by the QMRA than suggested by epidemiological surveys while predicting a lower number of infection, have also been shown by other studies (Havelaar et al., 2008). This points at the need for further cross-comparison between epidemiological surveys and QMRA with the ultimate goal to develop a standardised procedures to assess incidence and burden of diarrhoeal episodes and intestinal parasitic infections to make use of both tools.

4.3. QMRA limitations

Our model framework entails several limitations. The model relies on a range of assumptions pertaining to the volume of ingested water, the indicator to pathogen ratio and the number of exposure events, which were addressed in the uncertainty analysis and may lead to overestimation of the results. Especially the use of pathogen ratios is a key limitation, as *E. coli* counts may not reflect the densities of enteric virus in water bodies accurately (O'Toole et al., 2014). The dose-response models applied in this model are based on feeding studies (e.g. norovirus) or rely on epidemiological evidence (e.g. *Ascaris* spp.) conducted with healthy individuals in high income countries. Thus, dose-response may be considerably different due to acquired immunity related to exposure history or vaccination (Haas et al., 2014; Havelaar and Swart, 2014). The simplification of allowing no immunity after an exposure event in the QMRA may result in an overestimation of the disease burden (Haas et al., 2014). Certain pathogens, such as rotavirus, may have considerable different health impact in different age classes, which have not be taken it to account in this QMRA (Sigei et al., 2015). The helminth eggs in water can vary greatly as seasonal and clustered transmission of helminths is common (Cairncross et al., 1996). The model excluded exposure pathways such as dermal contact and inhalation and people living in a slum-like environment may also be exposed to contaminated drinking water and greywater, which should be taken into account in future QMRAs (Howard et al., 2006; Machdar et al., 2013). Further, it is known that in Kampala other pathogens such as adenoviruses, hepatitis A virus, *Vibrio cholerae*, hookworm and *S. mansoni* are present in the environment (Bwire et al., 2013; Katukiza et al., 2013); these were not included in the model although they can cause diarrhoea and other adverse health effects (Karagiannis-Voules et al., 2015; Fuhrimann et al., 2016).

4.4. Sensitivity analysis

In the sensitivity analysis we showed a considerable effect of different volume of water accidentally ingested. These values might, however, not be very accurate as exposure to wastewater very much depends on individual behaviours in the given environment and is also influenced by age, sex, level of education and socio-economic status (WHO, 2006; Haas et al., 2014). Clearly, there is a need to generate specific estimates for accidental ingestion of water during different exposures in low-income countries in the global South. In absence of valid information on the pathogenic strains, assumptions were drawn based on published ratios between *E. coli* and the pathogenic strain. We showed that especially values for rotavirus, *E. coli* and *Campylobacter* have a considerable effect on the total number of gastroenteritis cases. Studies have reported that temporal and spatial variation of environmental pollution is common in urban wastewater systems (Ensink, 2006; Katukiza et al., 2013; Fuhrimann et al., 2015). Furthermore, the *E. coli* to pathogen ratio might change over time as *E. coli* is secreted by humans and animals continuously, whereas pathogens are secreted only by a proportion of infected people over a short period of a few days (Mara, 2004).

4.5. Proposed mitigation strategies for exposure scenarios

In view of our findings, and acknowledging inherent limitations, a set of options for reducing disease burden for each of the five exposure groups are proposed (from highest burden to lowest burden). Importantly, the choice of the appropriate mitigation strategy needs to take into account cost-effectiveness as well as acceptability in concerned population groups (Machdar et al., 2013).

- $S_{playing}$: in order to protect children (<15 years) living in slum communities, oral rotavirus vaccination could be added to the Ugandan immunisation schedule and given to children at the age of >6 weeks (The Republic of Uganda, 2012; UNAS, 2014). This may be supplemented with bi-annual hygienic and deworming campaigns at schools, as well as at the level of households for targeting women of childbearing age (WHO, 2011b; Sigei et al., 2015).
- $S_{farming}$: the health of farmers working in the Nakivubo wetland can be promoted by means of farmer field schools. For example, in workshops on occupational health risks the value of personal protective equipment and the importance of sanitation and personal hygiene can be introduced (Van Den Berg and Takken, 2007).
- $S_{working}$: sanitation workers employed by the NWSC and those working for the PEA could be trained on the recognition of health risks and effective use of personal protective equipment. Moreover, bi-annual hygienic and deworming campaigns could be implemented (Van Den Berg and Takken, 2007; Strande et al., 2014).
- $S_{flooding}$: slum dwellers living in close proximity to the Nakivubo wetland could be protected against flooding events through the construction of small dams and drainage systems. In addition, access to frequently flooded areas along the Nakivubo channel might be restricted via perimeter fences (Katukiza et al., 2010).
- $S_{swimming}$: swimmers at the local beaches along the Inner Murchison Bay (e.g. Miami Beach, Ggaba Beach, KK Beach) could be informed about the risks involved with swimming in Lake Victoria (e.g. warning signs at unsafe places). Regulations

to restrict swimming at certain commercial beaches close to the discharge point of the Nakivubo Channel could be introduced and the beach water quality could be monitored on an ongoing basis (Soller et al., 2015).

Some general recommendations to reduce the exposure of the population to pathogens in contaminated water, proposed by others, are (i) re-establish the Nakivubo wetland flora to reclaim its function as a natural maturation pond and retention pool to protect the Murchison Bay in Lake Victoria (Mbabazi et al., 2010; Fuhrimann et al., 2015); (ii) fight faecal contamination of slum areas by promoting sanitation coverage in combination with safe collection, treatment or disposal of faecal sludge (Fuhrimann et al., 2016); and (iii) in the longer term, increase wastewater treatment and reuse capacity of Kampala city (Strande et al., 2014; Fuhrimann et al., 2015).

5. Conclusions

By using a QMRA approach, we estimated high risk, and considerable burden, due to water-borne pathogens among different population groups being exposed to wastewater in Kampala. Disease burden was estimated to be highest in children living in slum communities and in urban farmers with 0.199 and 0.06 DALYs pppy, respectively. Indeed, the DALYs pppy for these two population groups were several thousand fold above the revised WHO tolerable level of 0.0001 DALYs pppy. Hence, exposure to wastewater is anticipated to have considerable public health implications, calling for action to reduce *E. coli* and rotavirus infection, which were found to be of major concern. The presented QMRA provides a case study on how the risk assessment framework of the WHO guidelines for the safe use of wastewater, greywater and excreta can be applied to fit an urban low-income setting. The QMRA framework was built on context specific data of indicator microorganism and recent burden estimates for the most common water-borne pathogens resulting in gastroenteritis in Uganda. We showed the need to further link QMRA and epidemiological studies and to elaborate on how to assess the number of exposure events, the indicator organism to pathogen ratio and the dose-response relationship. Such risk assessment frameworks can make an important contribution to our understanding of health impacts in different population groups related to specific exposures, and thus promote the development of targeted mitigation strategies in resource-constrained settings.

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