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Can We Swim Yet? Systematic Review, Meta-Analysis, and Risk Assessment of Aging Sewage in Surface Waters

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Supporting Information

ABSTRACT: This study investigated the risk of gastrointestinal illness associated with swimming in surface waters with aged sewage contamination. First, a systematic review compiled 333 first order decay rate constants (k) for human norovirus and its surrogates feline calicivirus and murine norovirus, *Salmonella*, *Campylobacter*, *Escherichia coli* O157:H7, *Giardia*, and *Cryptosporidium*, and human-associated indicators in surface water. A meta-analysis investigated effects of sunlight, temperature, and water matrix on k. There was a relatively large number of k for bacterial pathogens and some human-associated indicators ($n > 40$), fewer for protozoan and ($n = 14-22$), and few for human norovirus and its *Caliciviridae* surrogates ($n = 2-4$). Average k ranked: *Campylobacter* > human-associated markers > *Salmonella*> *E. coli* O157:H7 > norovirus and its surrogates > *Giardia* > *Cryptosporidium*. Compiled k values were used in a quantitative microbial risk assessment (QMRA) to simulate gastrointestinal illness risk associated with swimming in water with aged sewage contamination. The QMRA used human-associated fecal indicator HF183 as an index for the amount of sewage present and thereby provided insight into how risk relates to HF183 concentrations in surface water. Because exposure to norovirus contributed the majority of risk, and HF183 k is greater than norovirus k, the risk associated with exposure to a fixed HF183 concentration increases with the age of contamination. Swimmer exposure to sewage after it has aged ∼3 days results in median risks less than 30/1000. A risk-based water quality threshold for HF183 in surface waters that takes into account uncertainty in contamination age is derived to be 4100 copies/100 mL.

INTRODUCTION

Surface waters, including fresh, estuarine, and marine waters, serve as drinking water sources, sites for recreation, sources of food, and essential organism habitat. They are susceptible to microbial pollution[1−5] from runoff,[6] animal feces,[7] and sewage discharges.[8] Microbial pollutants include pathogenic protozoa, viruses, and bacteria. Microbial pollution around the world is routinely assessed using concentrations of fecal indicator bacteria (FIB) including *Escherichia coli* and enterococci as proxies for pathogenic organisms.[9] FIB presence in bathing waters is linked quantitatively to gastrointestinal illness risk in swimmers when the FIB source is runoff, sewage, or wastewater effluent.[10−14] However, FIB can be found in a variety of sources including animal feces and environmental reservoirs[15−17] making them nonideal indicators. Therefore, new indicators that are fecal source-associated have been recently developed. For example, human-associated fecal indicators like HF183 and HumM2[18−21] are highly abundant in, and specific to, human feces.

Once introduced to surface waters, microbial pollutants are transported and dispersed, and removed from the water column by a variety of processes including inactivation.[22] Inactivation of microbial pollutants in surface waters can occur via light and dark pathways. Inactivation via dark pathways is caused by lack of nutrients, stress, senescence, and exposure to extracellular biocidal compounds as well as grazing by bacterivorous organisms.[22,23] Inactivation can also occur via light pathways where photons from the sun induce die-off directly (for example UVB damaging genomic DNA) or indirectly via reactive species (generated when photons interact with sensitizers like humic acids).[24,25]

Several recent studies have compiled inactivation data on *Escherichia coli* and enterococci, as well as human-associated indicators and pathogens in surface waters.[26−29] However, a systematic screening of the literature on pathogen and human-associated indicators suggested that available data are considerably more extensive than reported in these studies. A quantitative synthesis of available inactivation data of waterborne pathogens and human indicators would facilitate the modeling of these organisms in surface waters by providing a range of relevant decay rate constants.[30] Such data would also be useful in quantitative microbial risk assessment (QMRA) scenarios where fecal contamination may be aged.[31]

QMRAs have been used extensively to explore how risk of enteric illness varies with bathing water exposure to microbial pollution. For example, QMRA was used to show that swimming in water containing enterococci from different fecal sources, including gull feces, cow feces, and sewage, is associated with different risks[32] owing to the fact that different

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pathogens, with different pathogenicity, are present in the different fecal sources. Other bathing water QMRA applications allowed calculation of risk-based water quality thresholds for human-[33] and gull-associated indicators[34] for recreational waters; when concentrations of the human- and gull-associated indicators are below the risk-based thresholds, then water is safe for swimming. In these QMRAs, however, the fecal source was assumed to be "unaged", meaning that the ratio of indicators to pathogens in the fecal source material, an important model input, was assumed to be the same as that in the surface water. In reality, once introduced to the environment, the indicator and pathogens may decay at different rates, thus altering their ratios.

In this study, a novel systematic review and meta-analysis of decay rate constants for key pathogens and human-associated indicators was conducted. Target-specific decay rate constants were summarized as statistical distributions so they may be readily used in a variety of modeling applications. We subsequently used the decay rate constants in a QMRA to investigate how exposure to fecal contamination from untreated sewage of different ages during swimming affects the resultant gastrointestinal illness risk. The QMRA provides a framework for identifying a risk-based water quality threshold for the human-associated fecal marker HF183.

MATERIALS AND METHODS

Systematic Review. The systematic review and meta-analysis followed PRISMA guidelines.[35] The goal of the review was to compile from the peer reviewed literature quantitative information on the decay of waterborne pathogens and human-associated indicators of fecal pollution in surface waters under environmentally relevant conditions. Pathogens included in the review were human norovirus, *Campylobacter*, *Salmonella*, *Giardia*, *Cryptosporidium*, and *E. coli* O157:H7. Human norovirus surrogates in the *Caliciviridae* family, feline calicivirus and murine norovirus, were also included. Human-associated fecal indicators included were BacHum-UCD, HumM2, and HF183. These organisms were included as they were central to our planned QMRA application.

Web of Science core collection (search field = topic), Scopus (search field = article title, abstract, keyword), and PubMed (search field = all fields) were searched in August 2017 (Tables 1 and S1 of the Supporting Information, SI). The search terms were "(X) AND (water OR seawater OR stormwater) AND (die-off OR persistence OR survival OR inactivat* OR decay)" where X is the target-specific text (Table 1). Identified articles were assembled and duplicates were removed. Details of the review process, which involved two independent full text reviews of papers, are provided in the SI. The inclusion criteria were the paper: (1) contains quantitative data on the decay of the target of interest in raw (unaltered) surface water, (2) is in English, (3) is not a review, presents primary data, and is peer reviewed, (4) does not contain data solely on disinfection treatments such as addition of oxidants or SODIS, (5) included data from decay experiments where the temperature is greater than 4 °C and less than 30 °C, and (6) describes methods to enumerate the target that are logical and justifiable.

Decay rate constants were extracted from papers by a single reviewer. First-order decay rate constants (k), in units per day (d^{-1}), calculated from natural log (ln)-transformed concentration data as used in Chick's law,[36] were sought. If a study presented k values, then they were extracted from the paper along with any reported errors and model fit values (R^2 and/or

Table 1. Summary of Systematic Review Process[a]

target	date of search	target-specific search term	number unique papers identified through databases	number papers identified from references of review or other papers	total number papers screened	number for full text review	number included
Human norovirus	8/1/17	(norovir* OR norwalk vir* OR calicivir*)	857	8	865	50	2
Campylobacter	8/10/17	(campylobacter)	608	0	608	50	9
Salmonella	8/24/17	(salmonella)	3064	3	3067	75	25
E. coli O157:H7	8/24/17	("E. coli O157:H7" OR "Escherichia coli O157:H7")	762	11	773	44	15
Giardia	8/24/17	(Giardi*)	624	3	627	25	2
Cryptosporidium	8/24/17	(Cryptosporidi*)	1121	6	1127	53	7
Human associated fecal indicator	8/25/17	("human Bacteroides" OR "microbial source tracking markers" OR HF183 OR (bth AND bacteroides) OR bachum OR bachum-UCD OR humbac OR BsteriF1 OR (gyrB AND fragilis) OR "human Bacteroidales" OR bacH OR humm2 OR "human marker" OR "human-associated marker")	55	10	65	34	17
Murine norovirus	8/1/17	(norovir* OR norwalk vir* OR calicivir*)	857	8	865	50	2
Feline calicivirus	8/1/17	(norovir* OR norwalk vir* OR calicivir*)	857	8	865	50	1

[a]"Number for full text review" is the number of papers for which full text review was performed. "Number included" is the number of papers containing decay data that fit our inclusion criteria. The target-specific search term was combined with the text in the methods for the literature search.

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Table 2. Untreated Sewage Concentrations for Reference Enteric Pathogens and the Human Marker (HF), and Dose-Response Relations, and $P_{illlinf}$ for Reference Enteric Pathogens[a]

organism/target	C_{i_sewage}	unit (refs)	P_{inf}	$P_{illlinf}$ (distribution)	refs
Salmonella spp.	[0.5,5][b]	CFU/L[131,132]	$1-(1+\mu/2884)^{-0.3126}$	0.17−0.4 (uniform)	133−135
Campylobacter	[2.9,4.6] +[b]	MPN/L[136]	$1-1-{}_1F_1(0.024,0.024+0.011,-\mu)$	$1-(1+\nu\mu)^{-r}$	137
E. coli O157:H7	[−1,3.3][b,d]	CFU/L[138]	$1-(1+\mu/48.8)^{-0.248}$	0.2−0.6 (uniform)	139−142
Cryptosporidium	[−0.52, 4.7][b]	oocysts/L[143−146]	$1-\exp(-0.09\ \mu)$	0.3−0.7 (uniform)	147
Giardia	[0.51,4.2][b]	cysts/L[145,148]	$1-\exp(-0.0199\ \mu)$	0.2−0.7 (uniform)	149,150
norovirus	[4.0,1.1][c]	copy/L[151]	$1-{}_1F_1\ (0.04,\ 0.04+0.055,\ -\mu)$	0.3−0.8 (uniform)	152
HF183 (HF)	[5.2, 0.5][c]	copy/mL[33]	NA	NA	

[a]Unit is the unit of concentration in sewage, μ is the dose, P_{inf} is probability of infection, $P_{illlinf}$ is probability of becoming ill after infection. Note that units of pathogens is per liter and for HF is per mL to reflect the units used in the literature for these parameters. ${}_1F_1$ is the hypergeometric function. When specified, $P_{illlinf}$ are represented by a range of parameters, as indicated, drawn from a uniform distribution. $P_{illlinf}$ for *Campylobacter* is dose-dependent with $r = 2.44 \times 10^8$ and $\nu = 3.63 \times 10^{-9}$. References (Refs) for P_{inf} and $P_{illlinf}$ are provided in the last column. References for sewage concentration range are provided adjacent to the unit. [b]The two values separated by a comma are the minimum and maximum of the $\log_{10}$-uniform distribution. [c]The two values separated by a comma are the mean and standard deviation of a $\log_{10}$-normal distribution. [d]Lower range is not detected and −1 is used as a lower bound. P_{inf} and $P_{illlinf}$ are the same used by Boehm et al.[33] NA means not applicable.

root-mean-square error (RMSE)), and unit conversions were applied where appropriate. If a study reported decay model parameters from a model that was not a first-order model (for example a shoulder log−linear model, or biphasic model), then we extracted those reported model parameters and any associated errors and model fit values. If a study only reported T_{90} or T_{99} values (time to 90% or 99% reduction in concentration, respectively), then they were converted to first-order decay rate constants assuming Chick's law applied. If no first order decay rate constant was reported by the study authors, then Plot Digitizer (http://plotdigitizer.sourceforge.net) was used to digitize the concentration times series appearing in graphs within the publication. To be clear, this included data from studies that only reported decay model parameters from other types (not first-order log−linear) of decay models. k was then calculated as the regression slope of $\ln(C/C_o)$ versus time (in days) using linear least-squares regression in R. In this formulation C is the concentration at time t, and C_o is the concentration at the start of the experiment at $t = 0$. k and its associated error as well as model fit parameters were recorded. In carrying out the linear regression, values reported at or below the detection limit were included if and only if they were not preceded by other consecutive values at or below the detection limit; the value directly reported by the author was used in these cases.

Once all data were compiled, data sets and model parameters were examined to assess whether a nonlinear model was needed to describe decay. The goodness of log−linear model fit to the data (R^2 and RMSE), and the number of data points that appeared to "deviate" from the log−linear model were considered. In general, if R^2 values were greater than 0.7 and RMSE was relatively small (∼1 ln unit), only one data point visually deviated from a straight line fit between time and $\ln(C/C_o)$, or the non-log−linear model fit was no better than the log−linear fit, then a log−linear curve fit was deemed acceptable.

In addition to extracting information on the decay of the target of interest, whether the experiment was conducted in (1) freshwater, estuarine water, or seawater and (2) natural sunlight or the dark was also noted. If an experiment was reportedly carried out in sunlight, but at a depth in the water column greater than ∼25 cm or in a container that was opaque to UVA and UVB, then the experiment was categorized as carried out in the dark. This is justified by previous work suggesting that such experiments do not receive sufficient photons to be deemed affected by sunlight.[37] The temperature at which the experiment was conducted was also recorded. If a range of temperatures was provided, then the mean of the reported range was used. Finally, the method used for target enumeration was noted (culture, microscopy, quantitative PCR (QPCR), reverse-transcription QPCR (RT-QPCR), or propidium monoazide QPCR (PMA-QPCR)).

Twenty percent of the papers from which data were extracted by a single reviewer were randomly chosen for a second round of data extraction by a different reviewer. Data extracted by the two reviewers were compared to ensure consistency. A single author conducted detailed review of all data sets to identify missing data, data outliers, and data entry mistakes.

Meta-Analysis. Statistical distributions were fit to target-specific k values. Goodness of fit was assessed by visual inspection of residual and Q-Q plots. This yielded log-normal fits for all organisms/targets with the number of k values $n > 14$. For congruity, log-normal distributions were also used when $n < 14$ because there were too few values to justify a different distribution. A global linear model was used to model k as a function of target (categorical), temperature (continuous), water matrix (categorical: fresh = 0, estuarine = 1, and marine = 2), and presence or absence of sunlight (binary: dark = 0, sunlit = 1). Post hoc Tukey contrasts, which adjust for multiple comparisons, were used to assess whether k differed between targets. Results with $p < 0.05$ were considered statistically significant. Results where $p < 0.1$ are mentioned. All meta-analysis was conducted in R using the multcomp package.

QMRA: Exposure to Untreated Sewage of Known Age. A static QMRA was used to estimate GI illness risk from swimming in surface waters with varying concentrations of human-associated markers from untreated sewage of different ages using Matlab version r2017a (The Mathworks, Natick, MA). The influence of immunity and secondary transmission was not considered.[38] Swimmer exposure to microbially contaminated waters may also lead to other symptoms including respiratory illness and skin rash[39,40] that are not considered. In the QMRA, the human-associated fecal marker HF183 serves as an index for the amount of sewage present in surface water. Methods mirror those used by Boehm et al.[33] who established a risk-based threshold for HF183 for surface

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waters contaminated with unaged sewage. The QMRA uses reference pathogens norovirus, *Giardia*, *Cryptosporidium*, *E. coli* O157:H7, *Campylobacter*, and *Salmonella* as recommended by USEPA and used extensively in bathing water QMRAs.[32,41−43] The technique uses Monte Carlo simulations to randomly draw model parameters from their respective distributions for each model scenario.

Measured HF183 concentration (C_{meas}) in surface water serves as an input to the model and varies between 1 to 10^5 copies/100 mL in order-of-magnitude increments. Here we use 100 mL as the volume basis for the concentration as this is commonly used by beach managers. The age of the contamination (the time it has spent in surface water after being discharged from a sewage source) is τ. τ serves as a model input and varies between 0 (unaged) and 3 days (d) in 0.5 d increments. A total of 42 C_{meas}-τ combinations were modeled.

After C_{meas} and τ are specified, the concentration of i^{th} reference pathogen in surface waters ($C_{i\_surface}$) is determined as follows:

$$C_{i\_surface} = \frac{C_{meas} C_{i\_sewage}}{C_{hf\_sewage}} e^{\Delta k \tau} \quad (1)$$

where $\Delta k = k_{hf} - k_i$, and C_{i_sewage} and C_{hf_sewage} are, respectively, the i^{th} reference pathogen and HF183 concentrations in sewage, and k_i and k_{hf} are their first order decay rate constants (see SI for derivation). C_{i_sewage} and C_{hf_sewage} are described by distributions (Table 2), assumed to be independent, that were obtained from the literature and have been used in previous QMRA studies.[44,45] k_{hf} and k_i values in surface water were randomly drawn from their respective distributions (Table 3). In deriving eq 1, it is assumed that the advection and dispersion of HF183 and reference pathogens are identical, and any non-conservative behavior of targets is adequately captured by first order kinetics. During each model run, it was ensured that $F = C_{meas}\exp(k_{hf}\tau)/C_{hf\_sewage}$ (the volume fraction of sewage present in the water) did not exceed 1[45] and if it did, then new model parameters were drawn from their respective distributions. If $F \geq 1$ for more than 10% of the Monte Carlo draws for a particular C_{meas}-τ combination, the combination was deemed unrealistic (see SI for further details).

Table 3. Log_{10} Mean and Log_{10} Standard Deviations of the k Distributions (Distributions Shown in Figure S1)[a]

target	log_{10}-mean	log_{10}-stdev
HF183	0.063	0.34
HumM2	0.050	0.37
BacHum-UCD	−0.038	0.43
Salmonella	−0.17	0.51
Campylobacter	0.28	0.84
E. coli O157:H7	−0.43	0.37
Giardia	−1.36	0.96
Cryptosporidium	−1.39	0.80
Virus	−0.81	0.50

[a] k values have units of d^{-1}.

It is assumed that the volume (V) of water ingested by a swimmer per swimming event follows the log_{10}-normal distribution with a mean of 1.146 and standard deviation of 0.545; units of V are mL.[46] The dose of pathogen i, μ_i, is given by $C_{i\_surface}V$. The dose was used as input to the reference pathogen dose−response functions (Table 2) to determine the probability of infection (P_{inf_i}). The probability of illness (P_{ill_i}) was calculated by multiplying the probability of infection by the probability of illness given infection P_{illinf_i} (Table 2). P_{illinf_i} was randomly drawn from a uniform distribution for each model iteration except for the case of *Campylobacter* which used a dose-dependent formula (Table 2). The cumulative risk of illness from exposure to all reference pathogens (P_{ill}) is given by $P_{ill} = 1 - \prod_i (1 - P_{ill\_i})$. We assume that infection and illness for each pathogen is independent. 10 000 iterations were run for each C_{meas}-τ combination. The median, interquartile range, and 10^{th} and 90^{th} percentiles of P_{ill} for each C_{meas}-τ combination were calculated from the respective 10 000 iterations. P_{ill} was compared to the value 30/1000 which is approximately equal to the risk threshold published by USEPA for bathing water for a single swimming event.[12] A sensitivity analysis was completed following methods described by Julian et al.[47] (see SI).

QMRA: Exposure to Untreated Sewage of Unknown Age. The age of surface water contamination is usually unknown. We repeated the QMRA for a scenario where HF183 is measured in surface waters but the age is unknown. C_{meas} was specified as a model input at the same values used above. τ was drawn from a uniform distribution ranging from 0 to a maximum realistic value (τ_{max}) given the specified C_{meas} (derived in Results section). All other QMRA methods were the same as those above. 10 000 iterations were run for each C_{meas} to obtain distributions of P_{ill}.

RESULTS

Systematic Review of Human-Associated Fecal Indicators and Reference Pathogen Decay. This study identified a total of 333 experiments describing decay of the target pathogens and human-associated indicators in surface waters (Table S2). Here, "experiment" is defined as an experiment-target combination. Therefore, if researchers carried out one experiment and enumerated three different targets relevant to our review, this counted as 3 experiments (compiled data are provided in SI).

Only 24 of 333 decay profiles were not log−linear (7%); that is, they did not adhere to Chick's law. Of these 24, 16 decay profiles were for human-associated markers measured in a single study.[48] That study classified the decay profiles as "delayed" log−linear and provided k values but did not provide primary data. Thus, it was not possible to assess how divergent the data were from Chick's law. Given the small portion of decay profiles that were not log−linear, and for parsimony, first order decay kinetics were assumed to apply to all experiments. As described in the methods, first order decay constants (k) values were calculated for all the experiments if they were not provided by the authors. The exceptions were experiments from Green et al.[48] where we used k values they reported from delayed log−linear models.

Most decay experiments were conducted in freshwater (66%) with the remaining conducted in seawater (28%) or estuarine water (6%). Only 36 (11%) experiments were carried out under the influence of sunlight; the rest were carried out in the dark or under conditions where UVA and UVB were likely not able to penetrate. Experiments were carried out at temperatures between 5 and 28 °C. Across all 333 experiments,

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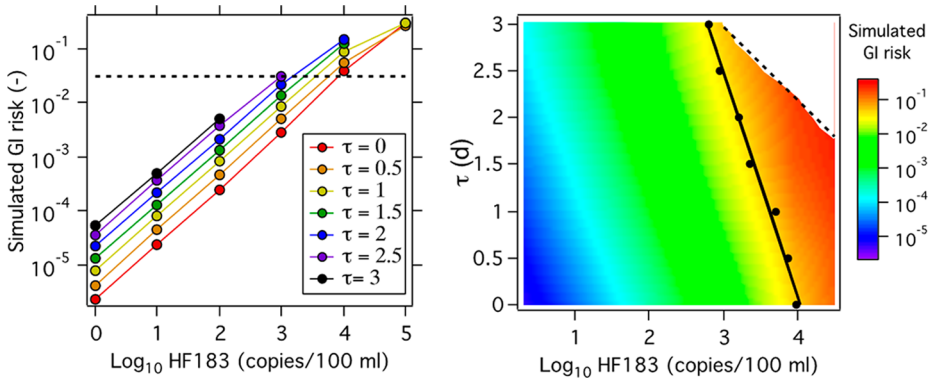

Figure 1. Left. Median simulated GI risk as a function of measured HF183 concentrations (C_{meas}) for contamination of different ages τ (units of day). Data points are not shown for HF183 concentration-age (C_{meas}-τ) combinations where F is greater than 1 in 10% or more of simulations. Horizontal dashed line shows 30/1000 risk threshold. Right. Median GI risk as a function of measured HF183 concentration (C_{meas}) and age of contamination (τ). Black circles show the 30/1000 risk for each τ, the solid line connecting them shows a linear regression for the 30/1000 risk contour. The white area shows unrealistic C_{meas}-τ combinations. The dashed line connects C_{meas}-τ combinations where $F \geq 1$ in more than 10% of the simulations. The solid and dashed lines intersect at τ = 3.3 d.

k varied from 0.015 d^{-1} to 220 d^{-1} with a median of 0.62 d^{-1}. Not a single experiment reported organism growth.

The number of experiments varied between targets. The bacterial pathogens *E. coli* O157:H7[49−62] and *Salmonella*[58,63−86] had the greatest number of k values (n = 84 each), followed by *Campylobacter*[63,86−93] (n = 41). The bacteria were enumerated using culture-based methods in nearly every experiment. The only exceptions were six *Salmonella* k values and six *Campylobacter* k values, which were measured using molecular methods (QPCR or PMA-QPCR).

Of the three human-associated indicators, HF183[48,94−105] had the greatest number of k values (n = 52) followed by humM2[48,94,96] (n = 15) and BacHum-UCD[94,99,106] (n = 13). All human-associated indicators were enumerated using molecular methods, and all were detected using QPCR with the following exceptions: 6 HF183 experiments used RT-QPCR and 2 BacHum-UCD experiments used PMA-QPCR.

There were fewer k values for *Giardia*[73,107] (n = 14) than for *Cryptosporidium*[73,108−113] (n = 22). *Giardia* was detected using microscopy while *Cryptosporidium* was detected using a variety of methods including cell culture and microscopy.

There were only 2 published decay rate constants for human norovirus, one for norovirus GI[114] and one for norovirus GII.[115] Both documented the decline in the number of copies of gene located at the ORF1/ORF2 junction using RT-QPCR. Culturable surrogates of human norovirus, murine norovirus[114,116] and feline calicivirus,[114] had only 4 and 2 k values, respectively. Of these, 2 and 1, respectively, were calculated using plaque assays (others were calculated using RT-QPCR).

k values for each organism were modeled as log-normal (Figure S1, Table 3). A linear model was used to assess whether human norovirus, murine norovirus, and feline calicivirus k differed between the viruses or measurement methods. The model indicated that there were no significant differences between k of the viruses, or between k measured by RT-QPCR or plaque assay. Therefore, k values from norovirus and its surrogates were combined and their distribution was approximated as log-normal (Figure S1).

Meta-Analysis of Decay Rate Constants. k values were aggregated into a single data set and a linear model was used to model $\log_{10}k$ as a function of temperature, water matrix, sunlight, and target. The target factor contained 9 categories (HF183, HumM2, BacHum-UCD, *Salmonella*, *Campylobacter*, *E. coli* O157:H7, *Giardia*, *Cryptosporidium*, and virus [human norovirus and its surrogates, aggregated]), which were coded using 8 "dummy" variables. Method type was not included as a variable because of method-target interactions (i.e., RT-QPCR for HF183 is not equivalent to RT-QPCR for norovirus, and not all methods applied to all targets). Sunlight, temperature, and various target dummy variables were significant variables in the global model (coefficients for sunlight and temperature were β_{sun} = 0.45, β_{temp} = 0.017, $p < 0.05$); water matrix was not a significant variable in the model.

Tukey contrasts tested the hypothesis that a target category had the same $\log_{10}k$ values as another target category, while controlling for variation due to other factors including sunlight and temperature. Several groupings of targets emerged that had similar $\log_{10}k$ values. $\log_{10}k$ of *Giardia*, *Cryptosporidium*, and virus were not different from each other ($p > 0.05$), but were significantly lower than $\log_{10}k$ of all other targets ($p < 0.05$) with two exceptions: $\log_{10}k$ of virus was lower but not significantly different from that of *E. coli* O157:H7 (p = 0.13) and BacHum-UCD (p = 0.09). $\log_{10}k$ of bacterial targets BacHum-UCD, HF183, HumM2, *Salmonella*, *Campylobacter*, and *E. coli* O157:H7 were not different from each other ($p > 0.05$), with one exception: $\log_{10}k$ of *Salmonella* was significantly smaller than $\log_{10}k$ of *Campylobacter* (mean difference of 0.33 $\log_{10}$ units, $p < 0.05$). $\log_{10}k$ of bacterial targets were significantly higher than that of the protozoan and viral targets excepting the relation with virus mentioned above (Figure S2).

Individual linear models for each target considered effects of sunlight, temperature, water matrix, and method (when applicable) as variables (see SI). Results are generally consistent with the global model. Method was only significant in the *Campylobacter* model and indicated that $\log_{10}k$ determined using molecular methods was smaller than those obtained using culture-based methods.

QMRA: Exposure to Untreated Sewage of Known Age. QMRA simulated the risk of gastrointestinal illness (hereafter "GI risk") for a specified measured HF183 concentration in surface waters (C_{meas}) and age of contamination (τ). We used log-normal distributions of target-specific k values (Table 3), and did not control for temperature or sunlight.

F was calculated for each C_{meas}-τ combination. Results indicated that some C_{meas}-τ combinations were unlikely (that

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is, $F \geq 1$ for more than 10% of the Monte Carlo draws) as they required that the surface water be comprised of over 100% sewage. For example, it is unlikely to find C_{meas} of 10^5 copies/100 mL in surface water contaminated with sewage after 1.5 days (Figure 1). We do not consider C_{meas}-τ combinations from the 7 (of 42) simulations in which 10% or more of the draws resulted in $F \geq 1$, leaving 35 realistic C_{meas}-τ combinations (Figure 1). Another way to interpret this is that given the concentration of HF183 in unaged sewage, and HF183 k values, there is an upper limit on C_{meas} as a function of τ. Linear interpolation allowed expression of the "$F \geq 1$ for more than 10% of draws" line as a function of C_{meas} and τ. Given the constraint that $F < 1$ in at least 90% of the Monte Carlo draws for a C_{meas} to be realistic at a given τ, $\tau < 5.33 - 0.79 \times \log_{10}C_{meas}$ where τ has units of d and C_{meas} units of copies/100 mL. Thus, the age of the contamination can be constrained by the measured HF183 concentration in surface waters.

The 10 000 simulations of GI risk for each of the 35 realistic C_{meas}-τ combinations are summarized in Figure S3 as box and whisker plots that illustrate the distribution of model outputs for each combination. Interquartile ranges are similar to those reported in other bathing water QMRA studies.[31,32] For simplicity, we use the median of simulated GI risk to describe results, although trends are similar for other percentiles. For a given τ, median GI risk increases as a function of C_{meas} (Figure 1). For a fixed C_{meas}, median GI risk also increases as τ increases. For example, when contamination is unaged (τ = 0 d), the median GI risk for $C_{meas} = 10^3$ copies/100 mL is ~3/1000. However, if the contamination is 2.5 d old, then the GI risk associated with exposure to $C_{meas} = 10^3$ copies/100 mL increases to ~30/1000. On the basis of a linear regression of median GI risk against C_{meas} and τ, the median C_{meas} above which risk exceeds 30/1000 (hereafter, risk-based threshold) is related to τ as follows: $\log_{10}C_{meas} = 4.0 - 0.42\tau$ (R^2 = 1.00) where τ has units of day and C_{meas} has units of copies/100 mL (Figure 1). This means that for each day that contamination ages, the risk-based threshold concentration of HF183 decreases by 0.42 $\log_{10}$ (copies/100 mL). Note that this equation is valid for $0 < \tau < 3.3$ d because after 3.3 d, the GI risk exceeds 30/1000 at C_{meas} that are unrealistic (that is $F \geq 1$ for more than 10% of the simulations; 3.3 d is τ where the lines representing the risk-based threshold and $F \geq 1$ in more than 10% of simulations intersect in Figure 1).

GI risk from exposure to norovirus alone is nearly equal to the risk from exposure to all reference pathogens at all τ considered (Figure S4). The risk from exposure to *Campylobacter* (τ = 0) or *Cryptosporidium* ($0 < \tau < 3$ d) alone is secondary to that from exposure to norovirus alone. A sensitivity analysis (see SI) found that the model is most sensitive to the following parameters: C_{noro_sewage}, C_{hf_sewage}, k_{noro}, V, and k_{hf}.

QMRA: Exposure to Untreated Sewage of Unknown Age. GI risk was modeled as a function of C_{meas} assuming the age of contamination was unknown, but could take on possible values between 0 (unaged) and τ_{max} where $\tau_{max} = 5.33 - 0.79 \times \log_{10}C_{meas}$ (see above). Median GI risk increased with C_{meas} (Figure S5), and interquartile ranges of predicted risks are similar to those obtained for the QMRA that considered specified ages (Figure S3). Assuming the age of contamination is unknown, the simulated median GI risk is 30/1000 (Figure S5) when C_{meas} = 4100 copies/100 mL. τ ranked the fifth most sensitive parameter behind V, C_{noro_sewage}, k_{hf}, and C_{hf_sewage} (Tables S6 and S7).

DISCUSSION

GI risk from swimming in water containing a fixed amount of sewage will decrease as the sewage ages and pathogen concentrations decrease. In this study, we used the HF183 concentration in surface waters as an index for the amount of sewage present. Using this approach, the HF183 concentration in surface waters can be used to estimate GI risk; and a risk-based water quality threshold for HF183 can be identified. We define the risk-based threshold as the HF183 concentration measured in surface waters for which the median simulated risk exceeds 30/1000, which is a risk threshold published by USEPA for bathing water.[12] Boehm et al.[33] derived a risk-based threshold for HF183 assuming that sewage contamination in surface waters was unaged. However, HF183 is not conserved in surface waters but rather decays over time. The present study sought to determine how the risk-based threshold for HF183 derived previously for unaged sewage contamination is affected by aging.

The risk-based threshold for HF183 in surface waters contaminated with sewage is weakly dependent on the age of contamination. When contamination is unaged, the risk-based threshold is ~9700 copies/100 mL (obtained by regressing $\log_{10}C_{meas}$ versus $\log_{10}$ median risk for τ = 0 d). The present study uses reference pathogen distributions in sewage updated with the most recent literature, resulting in a higher risk-based threshold for exposure to unaged sewage than reported previously (4200 copies/100 mL).[33] For each day of aging, the risk-based threshold decreases by ~0.4 $\log_{10}$ units. Therefore, for sewage contamination aged 2.5 days, the risk-based HF183 threshold is 900 copies/100 mL.

Other risk-based threshold definitions could be chosen. For example the HF183 concentration at which the 75th percentile of risk exceeds the 30/1000 could be used to be more conservative from a public health perspective. The same set of simulations could be executed using HumM2 or BacHum-UCD to determine their risk-based thresholds. Given the similar decay characteristics of the three human-associated indicators, the same dependence of the risk-based threshold on τ will be observed for HumM2 and BacHum-UCD.

Model results indicate that when sewage contamination in surface waters is over 3.3 d old, exposure to it is unlikely to result in a GI risk greater than 30/1000. This is due to the decline in pathogen concentration in surface water during aging. At the same time, the HF183 marker concentration in surface water, our index for the amount of sewage present, also declines. One can estimate an upper limit to the age of contamination (τ_{max} in units of days) from the HF183 concentration (units of copies per 100 mL) via the formula: $\tau_{max} = 5.33 - 0.79 \times \log_{10}C_{meas}$. This formula was derived by considering when more than 10% of the simulations for a particular C_{meas}-τ combination indicated that the surface water would need to be composed of more than 100% sewage. This upper limit assumes HF183 concentrations decrease due to first order decay and does not consider mixing and dilution, which are likely to occur.

The risk-based HF183 threshold decreases weakly with contamination age because norovirus contributes the most of all reference pathogens to the cumulative GI risk, and $\Delta k = k_{hf} - k_{noro}$ is positive, on average. On average, Δk for all pathogens considered herein except for *Campylobacter* is positive (see SI).

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As a result, the risk associated with exposure to the reference pathogens (except for *Campylobacter*) increases with τ for a given C_{meas}, whereas the risk associated with exposure to *Campylobacter* decreases with τ for a given C_{meas}. Given the similarities between k_{hf} and k of the other human fecal indicators, these trends will hold across the three human markers included in the systematic review.

The age of contamination in surface water is often unknown. We therefore estimated GI risk given the concentration of HF183 in surface waters assuming contamination age was unknown, yet constrained between 0 and τ_{max}. Interestingly, the sensitivity analysis indicated that the model output was less sensitive to the age of contamination than to other model parameters. The analysis suggested a risk-based threshold for HF183 of 4100 copies/100 mL when the age of contamination is unknown.

The change in the risk-based threshold with contamination age is controlled by Δk. There are a relatively large number of experiments documenting the decay of HF183 and bacterial reference pathogens in surface waters (over 40 for each), increasing confidence in their distributions. However, there are fewer experiments on the decay of protozoan and viral reference pathogens in surface waters. Data on norovirus decay are particularly sparse. Even when augmenting the human norovirus k with k from its surrogates from the same viral family (*Caliciviridae*), there are still only 8 virus k values with which to build a distribution. Decay characteristics tend to vary among viruses and depend on the makeup of the viral capsid and genomic structure,[117−119] making the use of surrogates distantly related to norovirus potentially unreliable. A systematic review of rotavirus decay rate constants in surface water found k ranged from 0.008 to 0.996 d^{-1} (median 0.056 d^{-1}),[28] similar to the range we found for norovirus and its surrogates (0.03 to 0.92 d^{-1}, median 0.196 d^{-1}). Future work is needed to better describe the decay characteristics of protozoan and viral pathogens in surface waters.

Overall, there is a paucity of studies documenting decay rate constants across all reference pathogens in seawater and estuarine waters, and in sunlight. With respect to sunlight, many studies do not document the absorbance of the surface water during experiments, and do not estimate fluence, making extension of those rate constants to other conditions difficult. Nelson et al.[25] describe best practices for reporting sunlight-mediated decay of microorganisms in surface waters. Additional experiments under diverse conditions of various surface waters will enable us to consider how the risk-based thresholds change under different environmental conditions (for example, in marine versus fresh water).

The meta-analysis found that increasing water temperature and presence of sunlight were linked to an increase in k, a result consistent with those reported in individual mechanistic studies of microbial decay[29,37,70,120] and a meta-analyses investigating temperature effects associated with *Salmonella*[29] and rotavirus[28] decay in surface waters. Given the increase in mean temperature expected over the next century due to climate change,[121] an increase in surface water decay of the pathogens surveyed in this study may be observed. However, increased decay of these pathogens may not coincide with a reduction in overall risk to swimmers, since increased frequency and intensity of rainfall induced by climate change[121] may lead to increased pathogen loading in surface waters,[122] and the relative importance of different human pathogens may change as their geographic ranges shift in response to changing temperature regimes.[123] Furthermore, Williamson et al.[124] describe precipitation-induced browning of surface waters due to climate change, reducing the potential for sunlight-mediated pathogen inactivation. The meta-analysis did not investigate how the source of organisms used in the experiments (for example, laboratory cultures versus sewage or feces), or the initial starting concentrations of organisms influenced decay characteristics.

This systematic review uncovered some unusual practices among researchers. Some report their organism decay profiles on graphs that to do not have systematic axis scales. In addition, researchers do not always clearly describe their experimental conditions with respect to lighting, salinity, temperature, or starting concentrations. Authors are encouraged to report these metadata clearly and to provide their raw data. Finally, many researchers report first order decay rate constants by estimating the slope of $\log_{10}(C/C_o)$ versus time. Technically, this is not a first order rate constant; the slope of $\ln(C/C_o)$ versus time is a first order rate constant.

There are limitations to this analysis. The clustering of k values by study was not considered in the meta-analysis. Some studies calculated more than one k value for one target or several targets while others reported a single k value for a single target. Due to the inconsistency in the number of k values reported across studies, controlling for clustering among studies was not feasible. k values for norovirus and its surrogates were combined to create a single distribution for norovirus k. While the analysis indicated that k was not different among the viruses and methods used to detect them, which supported combining them, the total number of k values was small. Third, the QMRA employed point estimates for single dose−response models for each pathogen, and therefore did not account for the variability of parameter estimates in these models or differences between various published dose−response models. For example, there are other norovirus,[125] *Campylobacter*,[126] and *Cryptosporidium*[127] dose response models that we did not consider herein. The choice of dose−response curves used herein mirror those used in projects that harmonize QMRA predictions with swimmer epidemiology study findings.[41,128] While exposure to norovirus commonly dominates QMRAs in recreational water, estimates of infectious norovirus concentrations and decay in environmental waters are highly uncertain due to the lack of a human norovirus culture system applicable for environmental media. Interestingly, a recent study confirmed infection by norovirus in swimmers after exposure to marine recreational waters supporting the importance of this exposure route for norovirus.[129] The QMRA considered reference pathogens using an approach that has been applied successfully in other bathing water risk studies and recommended by USEPA. However, there are other pathogens that may contribute to risk that we did not consider including enteroviruses, adenoviruses, and *Shigella*. The QMRA used the best available information at the time of model implementation, but is flexible and can be updated to reflect new findings on pathogen and indicator distributions, dose−response curves, and exposure assessments.[130] In addition, the QMRA considered a specific, simplified hazard, water contaminated with sewage, and thus the results should be cautiously extended to other hazards such as swimming in water contaminated by a mixture of diverse sources including treated wastewater effluent, animal feces, or microbial pollutants from "natural" sources including sand or wrack.

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USEPA suggests QMRA can be used to set site-specific recreational water quality standards.[12] The methods and results reported herein can be used to establish risk-based water quality thresholds for human-associated indicators in recreational waters by policy makers and managers. Methods, choice of model parameters, and decisions of how to define the risk-based threshold can be modified to match diverse policy goals.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.8b01948.

Figures S1−S5, Tables S1−S7, additional methods, data, and results (PDF)
(XLSX)
(XLSX)

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