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Review

Systematic review and meta-analysis of time-temperature pathogen inactivation

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ABSTRACT

Heat treatment, or thermal disinfection, is one of the simplest disinfection methods, and is widely used in the water, sanitation, and food sectors, especially in low resource settings. Pathogen reductions achieved during heat treatment are influenced by a combination of temperature and exposure time. The objective of this paper was to construct updated time-temperature pathogen inactivation curves to define "safety zones" for the reduction of four pathogen groups (bacteria, viruses, protozoan (oo)cysts, and helminth eggs) during heat treatment in a variety of matrices. A systematic review and meta-analysis were conducted to determine the times needed to achieve specified levels of pathogen reduction at different temperatures. Web of Science was searched using a Boolean string to target studies of heat treatment and pasteurization systems that exposed pathogens in water, wastewater, biosolids, soil, or food matrices to temperatures between 20 °C and 95 °C. Data were extracted from tables or figures and regression was used to assess the relationship between time and temperature. Our findings indicate that the temperatures and times needed to achieve a 1-$\log_{10}$ reduction of all pathogen groups are likely higher and longer, respectively, than previously reported. The type of microorganism and the matrix significantly impact T_{90} values reported at different temperatures. At high temperatures, the time-temperature curves are controlled by thermally stable viruses such as hepatitis A virus. Data gaps include the lack of data on protozoa, and the lack of data on all pathogen groups at low temperatures, for long exposure times, and with high $\log_{10}$ reductions. The findings from this study can be used by engineers, food safety specialists for the planning and design of engineered water, sanitation, and food pasteurization and treatment systems.

1. Introduction

Water and foodborne pathogens cause a variety of diseases including gastroenteritis, diarrhea, dysentery, hepatitis, cholera or typhoid fever (McCarton and O'Hogain, 2017), which are still the second-leading cause of mortality globally for children under five years old (WHO, 2017). Contaminated food, water and the lack of safe sanitation solutions are among the most important factors for these diseases (Prüss-Ustün et al., 2014). It is estimated that more than 2 billion people lack basic sanitation services around the world and 4000 children die each day on average due to diseases transmitted from contaminated water or human excrement (OMS and UNICEF, 2017). Unsafe food also causes a large disease burden, especially for populations that are elderly, immunocompromised, or under 5 years of age, with over 125,000 deaths per year (WHO, 2019). Soils are another potential route for pathogen transmission, especially where untreated sewage or fecal sludge are used in agriculture. Soil-transmitted helminths affect more than one-fourth of the world's population (Jourdan et al., 2018).

Heat treatment is one of the oldest and simplest methods used to disinfect water, sewage, biosolids, and food products. Exposure to high temperatures can result in the denaturation or coagulation of vital cellular components, causing loss of viability (Lund et al., 1996; Linden and Murphy, 2017). The use of pasteurization is widespread in the food industry (Juneja et al., 2014), thermophilic digestors are commonly used to treat sewage sludge (Lang and Smith, 2008; Aitken et al., 2005; Yin et al., 2016) and animal manure (Soupir et al., 2008) and high temperatures have also been proposed as a way to reduce concentrations of pathogens in water and wastewater (Carielo et al., 2017).

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The extent of pathogen reduction achieved in heated treatment processes is influenced by the combination of time and temperature (Mccann et al., 2009). Higher temperatures with shorter exposure times can achieve similar levels of pathogen reduction as lower temperatures with longer exposure times. There are trade-offs associated with these factors: higher temperatures require more energy for heating, but longer exposure times require larger reactors. Health outcomes associated with pathogens in water, food, and waste treatment systems can be better controlled with enhanced knowledge about the extent of pathogen reduction at different time-temperature combinations (Al-Holy et al., 2009).

In their seminal book on the health aspects of excreta and wastewater management, Feachem et al. (1983) published a time-temperature pathogen reduction curve, identifying a so-called "safety zone", that presumably guaranteed the elimination of pathogens. This information has been widely cited (Carielo da Silva et al., 2016; Linden and Murphy, 2017; Burch and Thomas, 1998; Aitken et al., 2005), but new studies published since 1983 present an opportunity to update this review. Also, the concept of a "safety zone" was not clearly defined in the original publication, and many of the papers cited in this study reported the "complete inactivation" of pathogens, or concentrations of zero pathogens in the treated product, without considering limits of detection for the methods used. This has resulted in uncertainty regarding the $\log_{10}$ reductions achieved at different time-temperature combinations, and confusion about how to use this information in practice, especially when moving toward a quantitative framework for assessing microbial risks. The problem with not specifying the pathogen reduction achieved in the "safety zone" is that if a quantitative risk assessment framework is used, depending on the initial concentrations of pathogens, different levels of reduction may be needed to achieve the target final concentration associated with a desired health outcome. As such, our goal was to update the time-temperature pathogen inactivation plot by identifying the $\log_{10}$ reductions achieved for different microbial groups at different time-temperature combinations and incorporating new data published since 1983 (Feachem et al., 1983).

Specifically, the objective of this study was to systematically review the literature to extract quantitative data on the reduction of pathogens and microbial process indicators in water, wastewater, biosolids, soil, or food matrices, due to heating alone at temperatures between 20 °C and 95 °C. We plotted the time-temperature combinations needed to achieve at least a 1-$\log_{10}$ reduction or at least a 3-$\log_{10}$ reduction, then used regression to analyze the data and produce a revised "safety zone" plot.

2. Materials and methods

2.1. Search strategy

Previously published guidelines and protocols for systematic reviews and meta-analyses were followed (Khan et al., 2003; Pullin and Stewart, 2006). The following research question was used to guide our review: *How long does it take to achieve a 1- to 3-$\log_{10}$ reduction of pathogens and indicator microorganisms at different time and temperature combinations?*

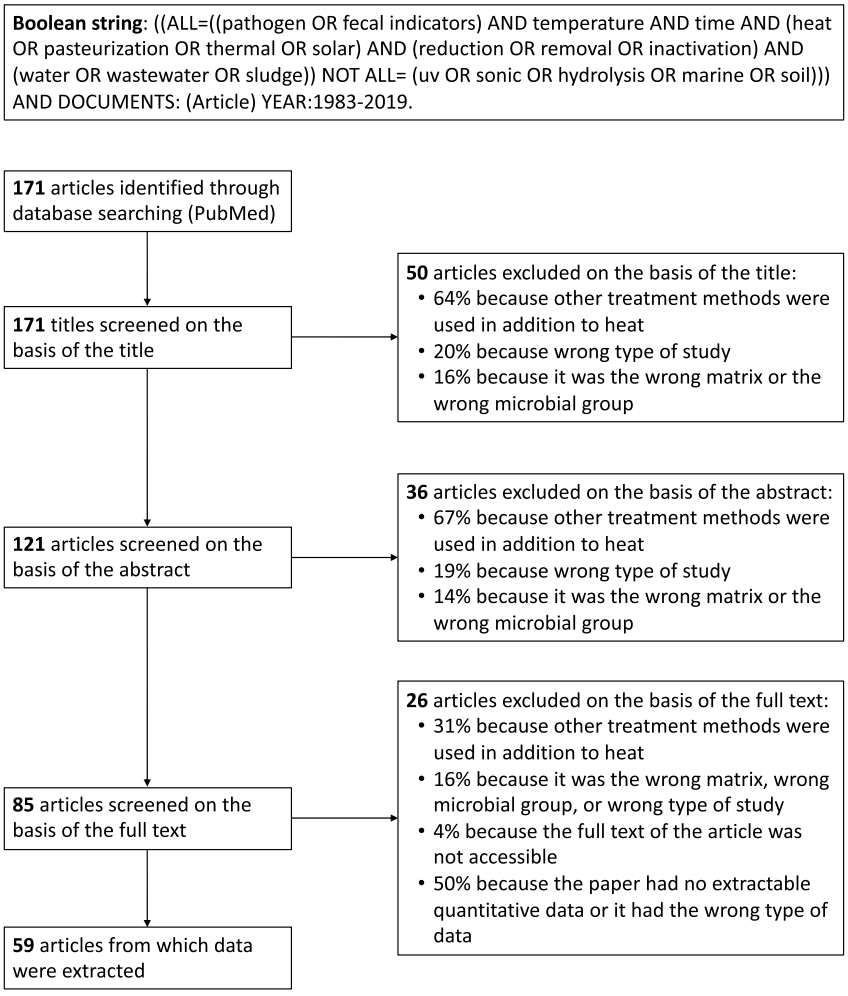

Fig. 1. Flow diagram of the systematic review of time-temperature combinations to reduce the levels of pathogens and indicators in water, wastewater, biosolids, soil, or food matrices.

Our target populations included viruses, bacteria, protozoa, and helminth eggs, including pathogens, fecal indicators, and microbial process indicators. We targeted studies of heat treatment and pasteurization systems used to treat water, wastewater, biosolids, or food matrices. We accepted experiments performed using purified matrices such as buffers, but we did not consider experiments with heat treatments that were combined with other types of treatment such as chlorination, UV radiation, photocatalysis, or sonication. Our goal was to obtain quantitative $\log_{10}$ reduction values achieved for different time and temperature combinations. The Web of Science database was searched using the Boolean string shown in Fig. 1, restricting the results to peer-reviewed articles published between the years of 1983 and 2019 in English, Spanish or Portuguese, based on the language proficiencies of the co-authors. References cited by Feachem et al. (1983), the Global Water Pathogen Project (Linden and Murphy, 2017) and other additional articles (Bertrand et al., 2012; Chen et al., 2017; Hosseini et al., 2017; Harroff et al., 2019; Sow et al., 2011; Manser et al., 2015) were also added to the list of reviewed papers.

2.2. Selection criteria

Articles yielded by this initial search were first screened based on the title. Articles were eliminated if they described other treatment methods used in addition to heat, if the title was not describing the target type of study, or if it was not targeting the target type of matrix or the target microorganism. Next, articles were screened based on the abstract. Articles were excluded unless all of the following applied: a) the abstract described a study of the inactivation or removal or reduction or decay of pathogens (virus, bacteria, protozoa, helminth eggs) or indicators; b) one of the following treatment processes was used: solar-heating, conventional heating, thermal treatment or pasteurization (papers describing treatments using heat combined with other treatment or disinfection processes were excluded); c) the matrices studied were: water, wastewater, compost, sludge, biosolids, food, or beverages; studies of marine water and soils were excluded (unless it was a study of biosolids-amended soil). The remaining articles were then screened by the full text. In addition to the criteria described above from the title and abstract review, articles were also excluded at this step if they did not contain the appropriate data needed to answer the main research question, or if they did not appropriately acknowledge or report the method's detection limit. Examples include articles reporting complete or 100% inactivation where only a sample of the population was assayed, without acknowledging the minimum number of pathogens that could be detected based on the effective volume sampled and other limitations associated with the methodology. The screening process was performed blindly by at least two co-authors, and there was an agreement of more than 90% of the papers. After the screening process, data were extracted from tables or from the text of the articles. If the data were not available in tables or the text, they were extracted from figures using WebPlotDigitizer v4.1 (Rohatgi et al., 2019; Drevon et al., 2017). All extracted data were organized in a spreadsheet with the following fields: microorganism name; temperature; time; $\log_{10}$ reduction value; matrix; and reference. If T_{90} values were not reported by the authors, they were calculated using the reported raw data. Exposure times were converted to hours and temperatures were converted to degrees Celsius (°C). Data from studies using temperatures above 95 °C were eliminated to avoid methods that involve boiling or steam sterilization.

2.3. Data analysis

The data gathered were plotted (time on the x-axis and temperature on the y-axis), and separate plots were made for data that fit into the following bins: 1-$\log_{10}$ reduction (e.g., T_{90} values); and greater than 3-$\log_{10}$ reduction. Multiple regression and Type III analysis of variance (ANOVA) was used to assess the relationship between log-transformed time, temperature, and the matrix (e.g., sludge, manure, compost, water, wastewater, buffers/media, and food matrices including meat products, beverages, and dry foods such as seeds and nuts) (see Table S1in Supplementary Material). The Bonferonni-adjusted outlier test (Fox and Weisberg, 2019) was used to check for outliers (as evidenced by Bonferonni p-values < 0.05), but none were found. The R script used to complete all statistical analyses and produce all figures is provided in the Supplementary Material. Individual log-linear regressions were also completed separately for each pathogen group, and the 95% predictive intervals for each significant regression with at least five data points and R^2 values greater than 0.6 were used to define the boundaries of the revised "safety zones." The 95% prediction limits for the regressions developed by Bertrand et al. (2012) for viruses were also added to the plots, for all viral groups with more than four data points ($N > 4$). Prediction intervals were not plotted for microbial groups with fewer than five data points, data from non-significant regressions, and data from regressions with R^2 values lower than 0.6, although the data were still plotted. After all analyses were completed, the upper 95% prediction intervals associated with the highest times for each temperature were used to construct the final boundaries that guaranteed either >1-$\log_{10}$ reduction or >3-$\log_{10}$ reduction.

3. Results and discussion

3.1. Study selection and characteristics

The systematic search initially yielded 171 articles. After screening, 59 articles were accepted for data extraction (Fig. 1). After including data from Feachem et al. (1983), the Global Water Pathogen Project (Linden and Murphy, 2017), and other articles identified in the references of the original search (Chen et al., 2017; Hosseini et al., 2017; Harroff et al., 2019; Sow et al., 2011), the data table contained a total of 363 paired values of time and temperature for different levels of $\log_{10}$ reduction. These data have been published as a CSV file to the Water Pathogen Knowledge to Practice (Water-K2P) Open Data Portal (Espinosa, 2015). In most of the articles, a D_{90} or T_{90} value (the time required to reduce the population by 90%) was reported (Spinks et al., 2006; Weiss and Hammes, 2005; Lang and Smith, 2008; Juneja et al., 2009; Soupir. et al., 2008; Stopforth et al., 2008; Aitken et al., 2007; Osaili et al., 2007; Aitken et al., 2005; Kenney and Beuchat, 2004; Juneja and Novak, 2003; Al-Holy et al., 2009; Tomat et al., 2015; Huertas et al., 2015; Elving et al., 2014; Juneja et al., 2012; Juneja et al., 2010a; Sharma et al., 2009; Kharel et al., 2018; Forghani et al., 2018; López-Romero et al., 2018; Karyotis et al., 2017; Vasan et al., 2013; Nygaard et al., 2012; Limcharoenchat et al., 2019; Linden and Murphy, 2017; Juneja et al., 2014; Luchansky et al., 2013; Syamaladevi et al., 2016; Burch and Thomas, 1998; Villa-Rojas et al., 2013; Palumbo et al., 1995). If this value was not reported, we calculated it using regression curves based on data reported in the paper. The majority of the data (61%) originated from experiments in food matrices (Palumbo et al., 1995; Osaili et al., 2007; Weiss and Hammes, 2005; Kenney and Beuchat, 2004; Juneja and Novak, 2003; Al-Holy et al., 2009; Tomat et al., 2015; Huertas et al., 2015; Mataragas et al., 2015; Juneja et al., 2012; Vidaček et al., 2011; Neetoo and Chen, 2011; Juneja et al., 2010a; Juneja et al., 2010b; Sharma et al., 2009; Kharel et al., 2018; Forghani et al., 2018; Taormina, 2014; López-Romero et al., 2018; Chandrakash and Davey, 2017; Karyotis et al., 2017; Park and Kang, 2013; Park et al., 2017; Shah et al., 2017; Syamaladevi et al., 2016; Becker et al., 2015; Weiss and Hammes, 2003; Luchansky et al., 2013; Vasan et al., 2013; Nygaard et al., 2012; Limcharoenchat et al., 2019; Kottapalli et al., 2019; Jeong et al., 2017; Cálix-lara et al., 2015; Juneja et al., 2014; Wiegand et al., 2009; McCann et al., 2006; Retzlaff et al., 2004; Juneja et al., 2009; Sow et al., 2011; Hosseini et al., 2017), though there were also data that originated from experiments in water, wastewater, compost, sludge, and other biosolids. A breakdown of the different matrices associated with the final extracted data table is shown in Fig. 2a.

The extracted data described the time-temperature inactivation for 21 different microorganisms, including viruses, bacteria, and helminths, some of which were pathogens and others were fecal or microbial process indicators. Microorganisms were pooled into the following ten groups: 1) *Salmonella* spp.; 2) *Listeria* spp.; 3) *Shigella* spp.; 4) *Pseudomonas* spp.; 5) *Enterobacter* spp. (*E. coli*, fecal coliforms, enterococci, and *Cronobacter*); 6) bacterial spores (*Bacillus* and *Clostridium*); 7) nematode eggs (including *Anisakis simplex* and *Ascaris*); 8) enteric viruses (including adenovirus, poliovirus, coxsackievirus, reovirus, and rotavirus); 9) parvovirus; and 10) bacteriophages. Bacterial groups were the most common microbial group in the reviewed articles (*Enterobacter* spp. and *Salmonella* spp. consisted of 39% and 30% of data points in the extracted data, respectively); viruses (enteric virus, parvovirus and bacteriophages) were the second most represented group (11% of all data points); followed by helminth eggs (3% of all data points) and surrogates of protozoa (e.g., bacterial spores), which had the least representation (only 2% of all data points). The breakdown of microbial groups in the final extracted data table is shown in Fig. 2b. Bertrand et al. (2012) cited data from additional studies on viruses, which are not all accounted for in Fig. 2, but were nevertheless used in this study to create the safety zone associated with a 1-$\log_{10}$ reduction.

Inactivation values reported are the result of the difference between initial and final microorganism concentrations. In the literature evaluated, microbial inactivation was quantified by culture methods for all bacteria, including colony counts and most probable number methods. In all studies on viruses, culture-based methods were also used (e.g., plaque assays, $TCID_{50}$). Authors of two studies included in this review reported using molecular-based methods such as polymerase chain reaction (PCR), but only to identify false positive results from culture-based methods (Aitken et al., 2007) or after finding no difference between the results from real-time PCR with reverse transcription and culture-based methods (Sow et al., 2011). All studies that focused on helminths eggs used microscopy and fluorescence techniques for enumeration.

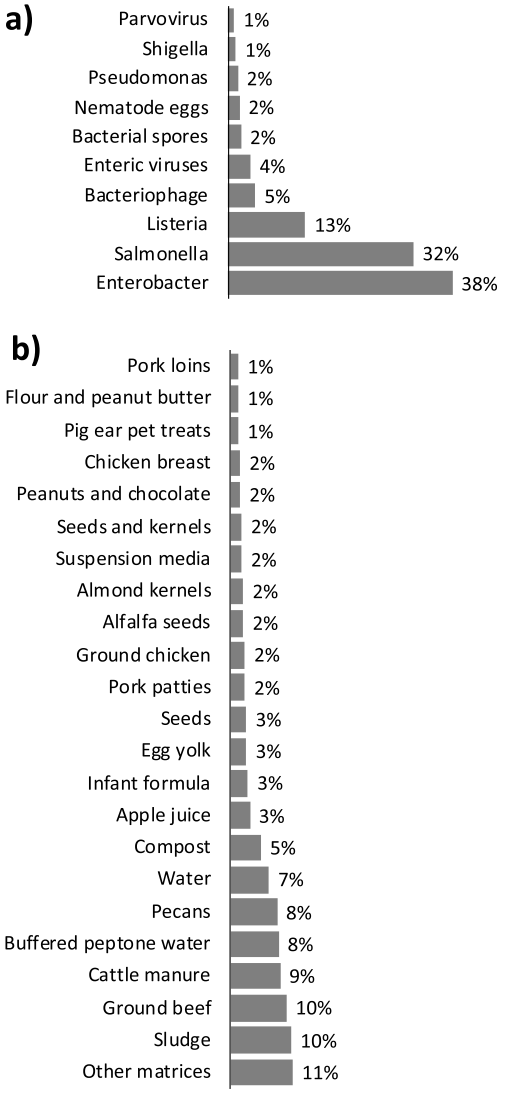

Fig. 2. A summary of the breakdown of extracted data with respect to: **a)** the types of matrices analyzed; and **b)** the groups of microorganisms analyzed.

3.2. Regression analysis

The multiple regression analysis of log-transformed T_{90} values with respect to independent variables microbial group, matrix, and temperature was significant ($p < 0.001$), with an adjusted R^2 value of 0.870. On average, T_{90} values were 3.4 h greater for viruses than they were for bacteria, and 3.8 h greater for helminth eggs than they were for viruses, after correcting for matrix and temperature effects. Type III ANOVA indicated that the log-transformed T_{90} values are significantly influenced not only by temperature ($p < 0.001$) and microbial group ($p = 0.0017$), but also by matrix ($p < 0.001$) (Table S2). After the removal of outliers, only data on bacteria and viruses were included in the final analysis. Thus, more research is needed on the thermal inactivation of helminth eggs and protozoa, to further develop our understanding of the effect of different matrices on pathogens from these groups.

Very few of the T_{90}-temperature data sets for the different microbial groups yielded significant regressions at the $\alpha = 0.05$ level, likely due to the limited number of data points for individual microbial groups. The coefficients of determination (R^2 values) for the temperatures associated with T_{90} values are summarized in Table 1. The regressions for *Listeria*, *Salmonella*, *Enterobacter*, bacteriophages, and nematode eggs were all significant ($p < 0.05$), but the *Listeria* and *Salmonella* regressions had R^2 values that were lower than 0.6. Temperature explained 89%, 79%, and 87% of the variability in the T_{90} values for bacteriophages, *Enterobacter*, and nematode eggs, respectively, and the prediction intervals for these three microbial groups were used to derive the safety zone for 1-$\log_{10}$ reduction (Fig. 3a). Temperature only explained 16% of the variability in the T_{90} values for *Salmonella*, likely due to the variety of different matrices used in the associated studies on *Salmonella* (see Table S1). Regressions for *Shigella*, *Pseudomonas*, parvovirus and enteric viruses were not significant ($p > 0.05$), highlighting the lack of data, the potential impact of matrix effects, and the uncertainty associated with achieving 1-$\log_{10}$ reduction of viruses due to heat alone. The resistance of enteric viruses to heat treatment is known to be highly variable, with significant differences in thermal inactivation having been reported between different strains of the same serotype of coxsackievirus isolated

Table 1
Coefficients of determination (R^2) for regressions fit to data from the different microbial groups using T_{90} values (time to achieve 1-$\log_{10}$ reduction).

Microbial Group	Slope	Intercept	N	R^2	p-value
Bacterial spores[c]	0.107	−14.204	7	0.533	0.062
Bacteriophage[b]	−0.256	14.976	5	0.893	0.015
Enteric viruses[c]	−0.039	0.985	9	0.033	0.641
Enterobacter[b]	−0.194	8.777	58	0.791	<0.001
Listeria[b,c]	−0.152	7.194	25	0.570	<0.001
Nematode eggs[b]	−0.411	21.051	10	0.874	<0.001
Parvovirus[a]	−0.108	8.266	3	0.983	0.084
Pseudomonas	−0.377	18.598	5	0.762	0.053
Salmonella[b,c]	−0.096	2.584	55	0.157	0.003
Shigella[a]	−0.477	24.11	3	0.985	0.078

[a] Fewer than 5 data points.
[b] Indicates that the regression was significant ($\alpha = 0.05$).
[c] $R^2 < 0.6$.

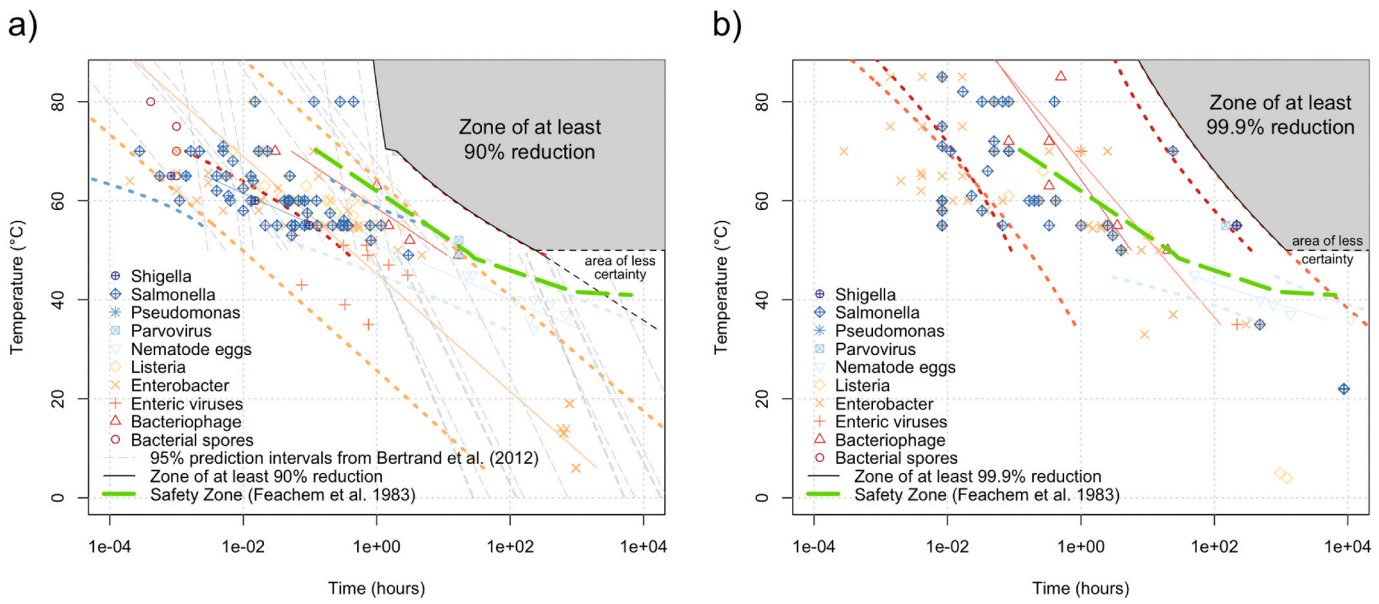

Fig. 3. Time-temperature curves developed for the inactivation of microorganisms using heat treatment to achieve at least: a) 1-$\log_{10}$ (e.g., 90%) reduction, b) 3-$\log_{10}$ (e.g., 99.9%) reduction. Solid lines show qualifying linear regression curves, and dotted lines show 95% prediction intervals, including the 95% prediction intervals for viruses using cell culture methods from Bertrand et al. (2012).

from the environment (Meister et al., 2018). For the >3 $\log_{10}$ reduction plot (Fig. 3b), regressions for enteric viruses, bacteriophages, *Enterobacter*, *Listeria*, *Salmonella*, and nematode eggs were all significant at the $\alpha = 0.05$ level, with R^2 values ranging from 0.262 (*Listeria*) to 0.956 (enteric viruses) (Table 2). There were not enough data to conduct regression analyses for the other microbial groups. The 95% prediction intervals for bacteriophage, enteric viruses, and nematode eggs were used in the $T_{99.9}$ plot (Fig. 3b).

3.3. Redefined "safety zones": time-temperature inactivation plots

All time-temperature data for each $\log_{10}$ reduction level are shown in Fig. 3, along with the lines of best fit and 95% prediction intervals for qualifying regressions. For reference, the original "safety zone" line published by Feachem et al. (1983) is also overlaid on both plots. Note that Feachem et al. (1983) described this line as the "conservative upper boundary for death," though it is not clear what this means in terms of $\log_{10}$ reductions, because many of those original papers reported non-detectable values at the end of the experiment and did not report detection limits for the methods used (as mentioned previously, these data were not used in our updated plots). The shaded regions shown in Fig. 3 indicate areas where the specified $\log_{10}$ reduction is achieved. The limits to this shaded region were drawn using the upper 95% prediction intervals for significant regressions with more than four data points and R^2 values greater than 0.6. The region bounded by temperatures of 37 °C and 50 °C is indicated as an area with less certainty, (shown with a dotted line on Fig. 3), given the conflicting findings reported by Feachem et al. (1983), Harroff et al. (2019), and Bertrand et al. (2012). It has been previously suggested that the guidelines developed by Feachem et al. (1983) and the US EPA (2003) are too conservative at these temperatures (Aitken et al., 2005; Popat et al., 2010; Harroff et al., 2019). Harroff et al. (2019) specifically recommended that the $T_{99.9}$ value for Ascaris can be predicted by the equation $T_{99.9} = (2.2 \times 10^9) \times 10^{-0.199T}$ (where $T_{99.9}$ is the time in days to 99.9% reduction and T is the temperature in °C). However, the 95% prediction interval for the T_{90} values for Hepatitis A virus reported by Bertrand et al. (2012), based on studies using cell culture methods, imply the potential need for longer storage times at these temperatures to achieve a 1-$\log_{10}$ reduction. Furthermore, Nappier et al. (2006) reported heat-resistant strains of F + RNA coliphages, suggesting that they could be appropriate indicators of the thermal inactivation of heat-resistant pathogens in thermophilic digesters. In general, there are few studies of pathogen reduction at temperatures below 50 °C, and a need to better understand the survival of different types of pathogens at these temperatures.

The $\log_{10}$ reduction zone plots shown in Fig. 3 are poorly aligned with the original "safety zone" plot constructed by Feachem et al. (1983). More specifically, the upper limits of 95% prediction intervals from the regressions indicate that higher temperatures and longer exposure times are required for a 1-$\log_{10}$ reduction compared to the original plot from Feachem et al. (1983), which was presumably an upper boundary for die-off. Variations in the T_{90} values for the same temperatures may be attributed to differences in the microbial groups, differences in the matrices used for the experiments, the growth phase of the cells, the methodologies used to quantify heat destruction, the recovery medium used to enumerate survivors (Juneja et al., 2009), the nutrients and fat content, water activity and mobility (Tadapaneni et al., 2018; Juneja et al., 2009), the chemical environment of the heating matrix and relative humidity (Lang and Smith, 2008; Tadapaneni et al., 2018), and other substrate effects such as adsorption, moisture content and pH (Elving et al., 2014; Spinks et al., 2006). The zone identified for achieving >3-$\log_{10}$ reduction (Fig. 3b) has even more separation from

Table 2
Coefficients of determination (R^2) for regressions fit to data from the different microbial groups for a >3-$\log_{10}$ reduction.

Microbial Group	Slope	Intercept	N	R^2	p-value
Bacterial spores[a]	–	–	1	–	–
Bacteriophage[b]	−0.122	7.81	7	0.681	0.022
Enteric viruses[b,a]	−0.146	9.915	4	0.956	0.022
Enterobacter[b,c]	−0.141	7.277	64	0.350	<0.001
Listeria[b,c]	−0.053	2.382	19	0.262	0.025
Nematode eggs[b]	−0.528	27.461	5	0.910	0.012
Parvovirus[a]	–	–	1	–	–
Pseudomonas[a]	–	–	1	–	–
Salmonella[b,c]	−0.169	9.509	46	0.511	<0.001
Shigella[a]	–	–	1	–	–

[a] Fewer than 5 data points.
[b] Indicates that the regression was significant ($\alpha = 0.05$).
[c] $R^2 < 0.6$.

the original "safety zone" plot, 10 °C–30 °C higher in most cases.

The zone identified to achieve a 1-$\log_{10}$ reduction has a shoulder at approximately 70 °C. Shoulders in the thermal resistance profile of viruses have been noted previously (Lomniczi, 1975; Adeyemi et al., 2017; Meister, 2019). It is well known that different viruses have different genome release and capsid melting temperatures (T_m) and virus inactivation mechanisms are different above or below these temperatures (Adeyemi et al., 2017; Meister, 2019). Furthermore, it has been reported that viruses repeatedly exposed to thermal disinfection can adapt greater resistance to heat treatment, which may increase the thermal stability of capsid proteins, increasing the viral capsid melting temperature (Dessau et al., 2012, Presloid et al., 2016; Adeyemi et al., 2017; Meister, 2019). Viral capsid melting temperatures may explain shoulders in Fig. 2a that occur between 50 °C and 70 °C. The RNA release and capsid melting temperatures of hepatitis A virus are generally above 70 °C for neutral to slightly acidic pH (Wang et al., 2015), which is higher than most enteric viruses. Bertrand et al. (2012) noted that few studies are published for thermal inactivation of viruses in the temperature range of 40–60 °C. This may be partly due to the wide variety of matrices used in these types of studies, as noted by Bertrand et al. (2012). Bertrand et al. (2012) also suggested lower virus sensitivity to thermal inactivation in complex matrices compared to simple matrices. More studies should be done to better understand the range of melting temperatures for currently circulating viruses, the mechanisms associated with pathogen decay at different temperatures and in different matrices, the influence of matrix effects on thermal inactivation, and the possibility of pathogen adaptation to heat treatment.

Fig. 4 shows a merged safety zone plot with four distinct zones, labeled Zones A, B, C, and D. Zone A corresponds to time-temperature combinations that provided greater than 3-$\log_{10}$ reduction for all microbial groups and matrices for which data were available (based on 95% prediction intervals). Zone B corresponds to time-temperature combinations that provided greater than 1-$\log_{10}$ reduction (based on 95% prediction intervals), but not necessarily as high as 4-$\log_{10}$ reduction, for all microbial groups and matrices for which data were available. Zone C is a zone of great variability, corresponding to time-temperature combinations that provide results that vary by orders of magnitude, depending on the microbial group and the matrix, ranging from 1-$\log_{10}$ reduction to more than 4-$\log_{10}$ reduction. For example, Lund et al. (1996) reported a 4-$\log_{10}$ reduction of bovine enterovirus in saline solution after 2.3 h at 55 °C, but Fu et al. (2014) reported a first order decay rate of 1.62 $days^{-1}$ for *Shigella* in a thermophilic anaerobic digester treating sewage sludge at 55 °C, which would equate to less than 1-$\log_{10}$ reduction even after 24 h. Finally, Zone D corresponds to time-temperature combinations that likely provide less than 1-$\log_{10}$ reduction for all microbial groups.

While the majority of the reviewed studies did not explicitly address matrix effects, differences between the physical-chemical characteristics of the different matrices used in the studies analyzed likely have an important impact on inactivation. These matrix effects may have different implications for different pathogen types. For example, the thermal inactivation of the bacteria *Bacillus subtilis* in three different food matrices was found to be more effective at lower pH, with variability in the inactivation kinetics observed between different types of foods (Jagannath et al., 2005). Alternatively, for hepatitis A virus in berries, a lower pH was observed to help aggregate virus particles, thereby increasing their resistance to thermal treatment (Deboosere et al., 2010). Fat content in the matrix is also considered to be important for *Salmonella*, with longer inactivation times anticipated for matrices with a higher fat content (Juneja et al., 2001). Among enteroviruses, higher salinity in liquid matrices enhances thermostability by up to 20 °C (Meister et al., 2020). However, the structure of viruses (enveloped vs. non-enveloped) was found to have no relationship on their thermal stability (Tuladhar et al., 2012).

3.4. Implications for practice

The reduction of pathogens at a particular temperature is highly dependent on exposure time (Kharel et al., 2018), matrix, and the microbial group. According to the data from our meta-analysis, at 60 °C, one day is necessary to achieve a 1-$\log_{10}$ reduction, but a temperature of nearly 80 °C is needed to achieve at least 3-$\log_{10}$ reduction of all microbial groups within a day. There is high variability in inactivation at very high temperatures, such as 80–90 °C. For example, 36 s at 80–90 °C was required to achieve a 5-$\log_{10}$ reduction of *Listeria* (Porto et al., 2004), and at 90 °C, *Salmonella* and *E. coli* experienced a >4 $\log_{10}$

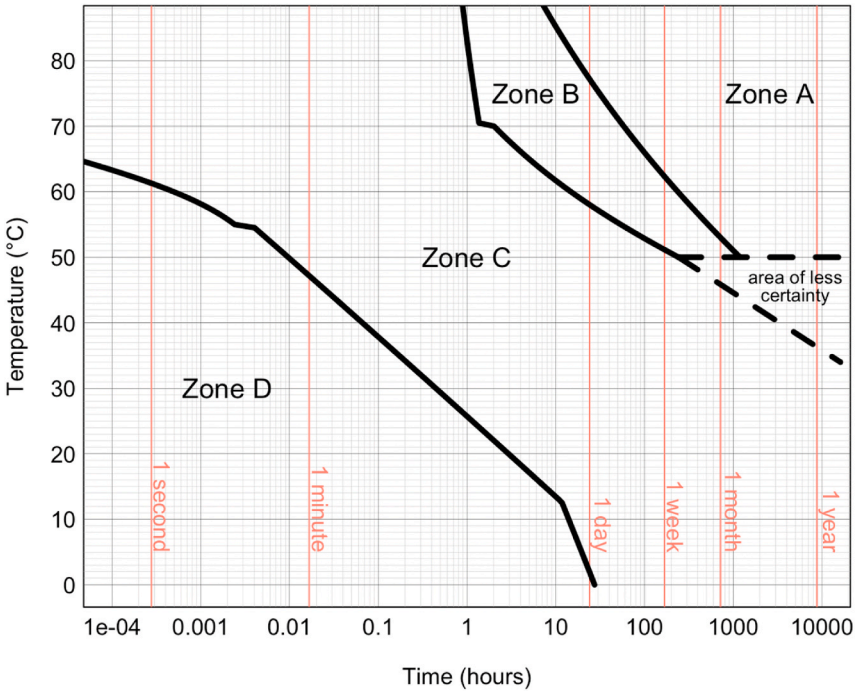

Fig. 4. Recommended time-temperature curve for pathogen reduction as a result of heat treatment, showing the thresholds needed to achieve specified $\log_{10}$ reductions. Zone A indicates time-temperature combinations that result in at least 3-$\log_{10}$ (99.9%) reduction for all microbial groups and all matrices; Zone B indicates time-temperature combinations that result in at least 1-$\log_{10}$ (90%) reduction for all microbial groups and all matrices; Zone C indicates time-temperature combinations that result in variable $\log_{10}$ reductions (<1-$\log_{10}$ for some microbial groups, >3-$\log_{10}$ for others); Zone D indicates time-temperature combinations that result in <1-$\log_{10}$ reductions for all microbial groups and all matrices. The area of less certainty may pertain to Zone A or Zone B, but there is limited data available in the literature.

reduction after 241 and 180 s, respectively (Kharel et al., 2018). Sow et al. (2011) reported a time of 180–300 s at 90 °C for >4-$\log_{10}$ reduction of hepatitis A virus and murine norovirus. Li et al. (2010) demonstrated that phages isolated from an engineered culture of *E. coli* were not inactivated at 90 °C, even after 45 min, indicating that viruses may be able to adapt to have high tolerance, even to very high temperatures. Virus adaptation to heat treatment has also been recently demonstrated by Meister (2019), Presloid et al. (2016), Zhao (2019), and Adeyemi et al. (2017). The US EPA (2003) suggested that the pasteurization of liquid sewage sludge at 70 °C for 30 min would reduce virus and bacteria concentrations to below detectable limits, and this process is approved for the production of class A biosolids under 40 CFR Part 503. Our findings suggest that this time-temperature combination may not necessarily guarantee >3-$\log_{10}$ reduction for all microbial groups. The data from this review suggest that heating to 80 °C for 1 h would provide >1-$\log_{10}$ reduction for all microbial groups and all matrices, but 1 day at 80 °C would potentially be required to achieve >3-$\log_{10}$ reduction for all microbial groups and matrices. Thermophilic reactors, typically operating at temperatures of 55 °C, would potentially need a retention time of up to 1 month to guarantee >3-$\log_{10}$ reduction of all microbial groups. These estimates are conservative, as they rely on the 95% prediction intervals from a rather limited data set, and they involved data from a variety of matrices.

3.5. Limitations

There are several limitations associated with our findings. First, there were few qualifying studies that reported data for viruses, protozoa and helminth eggs, even though they are more resistant to heat than bacteria (Aitken et al., 2005). There were also very few qualifying data with higher reduction values at lower temperatures. Additionally, while many of the papers identified in this review calculated T_{90} values using pseudo-first-order decay models, it has been shown that other models may be more appropriate for some microbial groups, due to effects such as shouldering (Mitchell and Akram, 2017). Some pathogens also have been found to exhibit a tailing effect under heat treatment before a 4-$\log_{10}$ reduction was reached (Meister et al., 2018).

4. Conclusions

We recommend the use of the time-temperature heat inactivation curve shown in Fig. 4. It represents conservative guidelines for achieving a desired reduction of pathogens when heat is the sole form of treatment. Caution should be taken when using this graph to design or plan treatment systems for different types of matrices, especially if using time-temperature combinations within Zone C, where there is considerable variability due to microbial group and matrix effects. Extra care should also be taken when interpreting portions of this graph associated with limited or conflicting data. More research is needed to fill in some of the data gaps, particularly related to protozoa and helminth eggs.

The following conclusions can be drawn from this study:

- Temperature, microbial group, and matrix explained 84.8% of the variance in T_{90} values for heat treatment between 6 °C and 95 °C
- A temperature of 80 °C is necessary to achieve reductions of at least 1-$\log_{10}$ within 1 h for all microbial groups and matrices
- Temperatures of 60 °C and 80 °C are necessary to achieve reductions of at least 1-$\log_{10}$ and 4-$\log_{10}$, respectively, within one day, for all microbial groups and matrices
- The inactivation of pathogens in mesophilic systems is likely to have very high variability, and may be limited unless exposure times are very high or other treatment methods are used in addition to heat
- There are considerable data gaps at low temperatures and long exposure times, especially for protozoa
- The best way to validate pathogen inactivation is through sampling and analysis, with consideration of the matrix and all associated environmental, physical or chemical factors that impact pathogen decay

Declaration of competing interest

No conflict of interest was identified related to this work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2020.113595.

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