

Opportunistic bacteria and mass mortality in ungulates: lessons from an extreme event

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Abstract. Mass mortality events in wildlife are a growing concern. Under conditions of rapid global change, opportunistic responses in bacterial commensals, triggered by environmental stressors, may be increasingly implicated in die-offs. In 2015, over 200,000 saiga antelope died of hemorrhagic septicemia caused by the pathogen *Pasteurella multocida* serotype B. We use this case to explore die-offs from commensal bacteria more broadly, looking at factors which might favor such extreme events. We review other recorded disease outbreaks caused by Pasteurellaceae organisms, firstly in saiga and secondly in other wild ungulates, and ask whether the 2015 die-off was unprecedented in terms of mortality rates, numbers dead, spatial scale, and in the nature of the predisposing or environmental factors involved. We also compare these outbreaks with mass mortality events associated with commensal bacteria in wildlife more generally. We identify three additional major die-offs in saiga in which Pasteurellaceae organisms may be implicated, of which one in 1988 closely resembles the 2015 hemorrhagic septicemia event. No other recorded cases in wild ungulates approach the magnitude of these cases for any of the metrics considered, possible exceptions being die-offs in Mongolian gazelles, in which the role of these pathogens is poorly substantiated. Environmental triggers were the most commonly suggested factor leading to pathogenesis, with warm humid conditions most commonly associated with hemorrhagic septicemia. Life history may also be significant—saigas are migratory and the largest pasteurellosis outbreaks outside this species also occur in migratory species of bird or other temperate ungulates aggregating in large numbers. Cases provoked by other commensals tend to be small in magnitude. Exceptions involve interactions between multiple pathogens and climatic conditions or sets of climatic conditions acting on different stages of the host–pathogen life cycle, leading to time lags between infection and subsequent disease. Overall, the scale and rapidity of the saiga die-offs appear unprecedented among mortality events caused by bacterial commensals in wild mammals. Experimental research into the genetics and microbiology of host–pathogen interactions upon changes in the external environment, and monitoring of animals and conditions at calving sites, may eventually reveal the underlying causes of these die-offs.

Key words: commensal bacteria; hemorrhagic septicemia; Kazakhstan; mass mortality event; opportunistic pathogen; Pasteurellaceae; saiga antelope.

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INTRODUCTION

Mass mortality events (MMEs) in wildlife are of increasing concern as human activity renders declining populations more vulnerable. There is some evidence that the frequency of such events may be rising (Fey et al. 2015) as host or range shifts bring new combinations of pathogens, hosts, and climatic conditions into contact (Harvell et al. 1999) or as climate influences host–parasite interactions in ways which cause higher rates of mortality (Rohr et al. 2013). In light of rapid global change and increases in environmental stressors, those bacterial commensals which become lethal pathogens under particular conditions, appear particularly likely candidates for an increasing role in disease and mortality. These organisms are opportunists, living apparently harmlessly in hosts for long periods of time and causing clinical disease when host immunity is compromised or following changes in the pathogen.

Evidence for the role of commensals as opportunistic pathogens in wildlife MMEs is scattered and has not so far been considered in a structured way. A particularly dramatic example occurred in saiga antelopes in 2015, and was attributed to *Pasteurella multocida* serotype B, in combination with climatic triggers (Kock et al. 2018). This example is unusually well documented and raises questions about whether this extreme case is an outlier; whether similar cases have occurred in the past; and what we may conclude about their likely frequency in the future.

In this paper, we ask whether the scale, mortality, and number dead in the 2015 event were unprecedented in comparison with other disease outbreaks in wild ungulates (including saigas) in which Pasteurellaceae organisms have been implicated, exploring the evidence for environmental and biological factors which may have played a role in the cases we review. Pasteurellaceae

infections occur across many vertebrate taxa, but ungulates feature prominently in the literature. By focusing on this group, we minimize variability in basic host biology and the pathogen strains to which they are vulnerable and therefore are able to draw out more generalizable lessons.

First, we introduce the saiga antelope and the 2015 mass mortality event which prompted this review. We then examine the Pasteurellaceae family and associated diseases of interest, as the relationships between these are complex and still poorly understood. We go on to review key characteristics of mass mortality events from different expressions of pasteurellosis in saiga and other wild ungulates worldwide, grouping these into cases of hemorrhagic septicemia and pneumonic pasteurellosis (which includes bovine respiratory disease), the two major syndromes associated with these pathogens in ungulates. We also ask whether the patterns observed for pasteurellosis in saigas and in other wild ungulates are similar to cases of this group of diseases in other taxa, or to MMEs caused by other opportunistic bacteria living as commensals in ungulates, focusing particularly on predisposing factors and the environmental conditions which favored these outbreaks. We end by considering what our review of case studies tells us about possible mechanisms behind the 2015 MME in saiga, identify significant gaps in understanding of this event and of Pasteurellaceae behavior more generally, and suggest future research directions to improve our knowledge of the mechanisms behind the shift from harmless commensal to lethal pathogen in these organisms.

METHODS

The information presented here on the 2015 die-off is based on our own primary field and laboratory research (Kock et al. 2018, Orynbayev

et al. 2019). Concerning the rest of the review, a number of literature searches were conducted, described in the following paragraphs.

Documented cases of pasteurellosis in wild ungulates

A primary literature search for detailed cases of die-offs in other ungulates caused by species of Pasteurellaceae was conducted in English (both UK and U.S. spellings), using the Google online search engine (both general and Google scholar) for references to hemorrhagic septicemia (HS), pneumonic pasteurellosis (PP), or the general term pasteurellosis, using the additional key words ungulate or wildlife. Similar searches were conducted substituting names of the syndromes for those of associated pathogens, *Pasteurella multocida*, *Mannheimia haemolytica*, and historical variations on these. Articles with abstracts in English but the main text in a foreign language were translated and reviewed.

Searches covered peer-reviewed articles, book chapters, conference proceedings, theses, and gray literature. The pathogens and their associated syndrome were first described scientifically in the 1870s in domestic fowl and livestock (De Alwis 1999). The earliest case we came across in wildlife was documented in 1911, so this is the effective start date of our review. The majority of retrieved sources were peer-reviewed articles, particularly from veterinary reviews; of the 15 primary articles describing outbreaks of HS, 14 were peer-reviewed journal articles and one a conference presentation. Some additional outbreaks with lower levels of detail and substantiation (from secondary sources) were also documented. Of the 11 primary articles describing PP cases, six were in peer-reviewed journals and five in conference proceedings (all at conferences specific to bighorn sheep (*Ovis canadensis*) conservation). Although many cases described as “mass mortalities in wildlife” concerned only a handful of animals, and in some examples the affected animals were only semi-wild, every case identified in the literature is included here except those in which only one or two individuals died. Additional articles relating to the described outbreaks which offer new data or insights (for example those describing the serotyping of organisms isolated from MMEs many years afterward) are also included in the review.

In the case of saiga, for which most primary literature on historical MMEs is in Russian, we sourced information from official saiga monitoring and disease investigation reports supplied as hard copies by the Institute of Zoology, Kazakhstan, and from Russian language scientific journals. We provide a relatively high level of detail on these sources in Appendix S1, as much of this material remains unpublished in English and unavailable outside unpublished reports. Because cases in many other north-Asian ungulate species are also available only in Russian, we also conducted a general search using the Russian version of the Google search engine, using the same terms used for the English search, but in the Russian language and script. Many sources identified online were not available electronically, so were obtained as hard copies from libraries in Moscow.

Based on our literature review of specific cases, we present data on mortality rate, numbers dead, temporal and spatial characteristics of outbreaks, and age and sex profiles of affected individuals, as well as discussing associated environmental factors and co-pathogens. This information is summarized in tables in the main body of the paper, with more detail provided in Appendices S2, S3.

Reviews of pasteurellosis in ungulates including domestic livestock

Going beyond papers focusing on specific cases, we also searched for more general publications covering pasteurellosis in ungulates. Most Russian sources, other than those on saiga, fell into this category. Although the conditions for transmission and development of pasteurellosis under farm or semi-captive conditions are very different from those in the wild, pasteurellosis is an important disease of domestic livestock and there is much to be learned from this literature. Here, we used the same terms listed above plus the words bovine respiratory disease, livestock, cattle, and buffalo. From the results, rather than selecting specific case studies, we selected papers and books reviewing the subject and statistical studies covering a large number of cases.

Genetics and microbiology of focus pathogens

The above search procedures also yielded reviews on the behavior, microbiology, and

genetics of the pathogens responsible for Pasteurellosis in ungulates and other taxa. This search was then expanded and refined using combinations of keywords for our focus syndromes and organisms, plus genetics, DNA, and microbiology. We selected those reviews which focused on the phylogeny and classification of *Pasteurellaceae* organisms, and on the genetics and bio-chemistry behind their virulence.

The impact of environmental factors on Pasteurellaceae organisms

Many publications identified through earlier searches contained information on environmental factors influencing pasteurellosis outbreaks or bacterial activity in the laboratory. We then conducted specific searches on these factors in order to ensure that we had not missed key papers or experimental work conducted in vivo. This was achieved by including search terms such as climate, weather, temperature, humidity, stress, nutrition, element, mineral, and immunocompetence along with the names of syndromes and pathogens as above. We did not specify host organisms in these searches.

Reviews and case studies on other opportunistic bacteria affecting wild ungulate species

In order to place our review in a broader context, we draw comparisons with mortality events caused by other gastrointestinal and upper respiratory tract bacteria in ungulates which live for long periods as commensals, yet also exhibit opportunistic responses to stress factors, leading to tissue invasion and death of the host (see Appendix S4 for details). In these cases, the non-exhaustive literature search initially focused on review papers, followed by acquisition of papers detailing specific cases considered to be salient for this paper. Lastly, we looked for examples of mass mortality events caused by opportunistic pathogens across all types of host taxa, focusing on those holding lessons about mechanisms through which environmental triggers may act and the role of host life history (as opposed to taxonomic classification) in disease etiology.

Limitations

Links between the presence of *Pasteurellaceae* organisms and disease cannot always be

confirmed post hoc, or from interpretations made in the literature. This is because, due to their commensal nature, these organisms may be present but invade the body only after death, thus being identified at post-mortem examination. Interactions with other pathogens, such as viruses and mycoplasmas, may also be crucial to understanding disease etiology and it is often unclear whether the *Pasteurellaceae* organism was the major or sole pathogen, or emerged as an opportunist following infection by other organisms (Besser et al. 2013). These factors make diagnosis difficult without a combination of high-quality pathology and histopathological data and laboratory-based identification of organisms to the species level (as done by Kock et al. 2018). These issues may have affected the conclusions drawn by some of the earlier studies reviewed here which, being dependent on culture alone, may have missed co-infections with organisms more easily detected by PCR, thus misidentifying *pasteurellaceae* organisms as sole or primary pathogens. Older Russian sources in particular often lacked sufficient information for full diagnosis. Distinct syndromes were not always identified, the blanket term of “pasteurellosis” being used in many cases to cover both septicemic and pneumonic forms, despite quite different etiologies. Overall, the use of English and Russian as primary search languages may have caused a bias toward cases from temperature zones, which formed the overwhelming majority of recorded cases. A further caveat is that in forest or mountain species, the total numbers dead or mortality rates may be unavailable or erroneous because many carcasses were never found. This is an issue because the perceived unprecedented nature of the saiga incidents lies in the high level of mortality; in these cases, relatively accurate carcass counts can be conducted from the air or ground over large areas, and so severe underestimation is less likely.

RESULTS

The saiga antelope: ecology and life history

The saiga antelope (*Saiga tatarica*) is a migratory ungulate found in the pre-Caspian and Central Asian steppes, with population ranges covering parts of Russia, Kazakhstan, and Uzbekistan and a sub-species (*S.t. mongolica*) in

western Mongolia. The three major saiga populations in Kazakhstan are shown in Appendix S1: Figure S1. In Kazakhstan, saigas are highly mobile, and cover huge areas during their seasonal migrations, mostly north–south following vegetation gradients (Singh et al. 2010). Females (with a few, mostly young, males) congregate in dense calving aggregations many thousands strong in May, the time of peak biomass production in the steppe. Calves are hidden for the first few days, but within 2–3 d are able to run, and within 10 d they and their mothers continue their spring migration (Kühl et al. 2007). The major known causes of large-scale natural mortality in saigas are heavy snowfall or freezing rain (known as *dzhut* in Kazakh), and diseases described under the umbrella term of pasteurellosis, recorded only in Kazakh populations (Bekenov et al. 1998, Sokolov and Zhirnov 1998) and which we explore in the following sections.

Historically, the species was very abundant, but large-scale hunting in the 19th century reduced its numbers substantially (Bekenov et al. 1998). Following a period of recovery and sustainable management for meat production during the Soviet period, saiga numbers were severely affected by poaching for horns and meat during the 1990s–early 2000s, leading to a decline in numbers of over 90% during a 10-yr period, and the species' listing as Critically Endangered on the IUCN Red List in 2001 (Miller-Gulland et al. 2001). Conservation efforts led to recovery in some populations, and one in particular, termed the Betpak-dala population, reached 242,000 in April 2015, which was about 65% of average number for that population during the 1980s (CMS 2015).

The 2015 mass mortality event.—In May 2015, the Betpak-dala population was affected by a mass mortality event leading to the death of around 210,000 animals, close to 88% of that population and 62% of the global population of the species (CMS 2015). The cause of death has been established as hemorrhagic septicemia, caused by *P. multocida* (Kock et al. 2018).

The outbreak occurred during the calving period, when saigas congregate in large groups. Mortality was recorded at fifteen calving aggregations scattered over a very large, remote landscape (see Appendix S1: Figure S2). Unaffected aggregations were not identified, but there was

a scattering of individual mortalities spread across the landscape and around 30,000 animals survived, based on post-mortality ground and aerial surveys. The dates of onset (first mortality) at each site ranged from 9 May to 29 May, but within each site onset was rapid; individual animals died over a period of hours following first symptoms, and mortality apparently reached 100% of adults within a week of the index case. Calves were initially unaffected, dying after their mothers, either from starvation or from ingestion of *Pasteurella* organisms from the milk. For this reason, transmission of a virulent form between animals via aerosol or feces cannot alone explain the epidemiology of this event. As other pathogenic organisms were not identified, and there was no contact between aggregations at the time, it is thus hypothesized that an environmental trigger, which must have been spatially widespread in the environment and temporally specific to the period just before onset, may have played a role in pathogenicity. Such a trigger may have affected the relationship between commensal bacteria and their adult saiga hosts, which carry them in the nasopharynx, as part of the microbiome (Kock et al. 2018).

Pasteurellaceae: typology, classification, and association with disease

Pasteurellaceae are a large family of Gram-negative bacteria, many of which live as commensal organisms in the upper respiratory tract of mammals and birds. Pasteurellosis is not a distinct syndrome. Different diseases may be associated with single or multiple species and strains of these organisms, and in this review, we focus on the most common manifestations of hemorrhagic septicemia (HS) and pneumonic pasteurellosis (PP). The most virulent strains of Pasteurellaceae organisms may act as primary pathogens in susceptible animals. However, many of these bacteria live in healthy carriers and act as secondary or opportunistic pathogens (Rudolph et al. 2007). Thus, while some of the die-offs reviewed here appear to be cases of introduction of a virulent strain of bacteria into a naïve population, others appear to have been at least partly triggered by some other factor increasing the virulence of Pasteurellaceae organisms or affecting the immune system in the host. In some cases, both

mechanisms may work together, as the spread of novel pathogens may also lower host immunity and trigger activity in opportunistic bacteria.

Pasteurella multocida.—Hemorrhagic septicemia, the proximate cause of the 2015 die-off in saiga, is most commonly reported in cattle and domestic Asian buffalo and is usually associated with *P. multocida* type B:2 (De Alwis 1999, Shivachandra et al. 2011, Wilson and Ho 2013). Acute disease appears following the multiplication of these bacteria in the respiratory tract, invasion across the mucosal membrane, and infection of internal organs. Laboratory inoculation suggests that following invasion, extremely rapid multiplication in the blood and host organs then results in death between a few hours and three days later (Bastianello and Henton 1994, Kharb and Charan 2012).

Different strains of *P. multocida* have been classified according to different systems and are associated with different diseases. In this review, we use the species names and serotypes (identified using specific phenotypic tests) given in the papers cited, as the relationship between these names and actual organisms has changed over time. The most widely used system is a combination of Carter's system of typing into five capsular serogroups (A, B, D, E, and F) and Heddlestone's somatic typing of 16 serotypes based on their lipopolysaccharide (LPS). Thus, isolate designations usually consist of a capsular serogroup letter followed by a somatic serotype number. In ungulates, HS cases outside Africa tend to be associated with the B capsular type.

In other taxa, *P. multocida* infections have been recorded in species as different as humans (Weber et al. 1984), elephants, and snow leopards (De Alwis 1999, Spickler et al. 2010) and are associated with various syndromes including septicemias (again, often associated with B capsular type), respiratory disease, and other rarer manifestations (De Alwis 1999). *Pasteurella multocida* A:1 and 3 are most commonly associated with avian cholera, although many more serotypes have been identified in birds (Friend 1981, Christensen and Bisgaard 2000) and capsular type D is associated with atrophic rhinitis in pigs (Wilson and Ho 2013).

More recently, DNA sequence-based techniques have started to replace the phenotypic methods for identification of Pasteurellaceae

species and biotypes (Townsend et al. 2001). Specific genes and factors associated with virulence (e.g., toxicity, resistance to phagocytes, surface adhesion, and iron uptake) have been described for certain disease manifestations associated with *P. multocida* (see Harper et al. 2006, Wilson and Ho 2013 for reviews). However, little is known about the mechanisms behind the initial stages of acute HS development. Over 90 genes specific to HS-causing strains have now been identified (Moustafa et al. 2015) and should help identify the specific virulence attributes of these strains in future. The bacteriology of saiga *Pasteurella multocida* isolates, including details of virulence genes present from the Kazakhstan outbreaks and occasional deaths, is now available (Orynbayev et al. 2019).

Mannheimia haemolytica and related organisms.—A group of Pasteurellaceae organisms once known as *Pasteurella haemolytica* are also associated with disease in ungulates. *P. haemolytica* was recently split into biotypes A and T based on the ability to ferment either arabinose or trehalose. T biotypes are now classified as *Bibersteinia trehalosi* and most A biotypes as *Mannheimia haemolytica*. A11 was given the name *Mannheimia glucosida* (Shivachandra et al. 2011). *Mannheimia haemolytica* is commonly associated with respiratory disease, grouped under the term pneumonic pasteurellosis (PP). One well-documented form, known as shipping fever, is linked to stress and poor air quality associated with closed transport of livestock in poorly ventilated spaces. As noted above, strains of *P. multocida* (usually serotype A:1) may also be implicated alongside this organism as the primary agent or sole detected pathogen in cattle (or more rarely sheep) pneumonia (see reviews in Harper et al. 2006, Mohamed and Abdelsalam 2008, Wilson and Ho 2013). Other species of bacteria and viruses also contribute to pathogenesis in many cases, for example in bovine respiratory disease (Taylor et al. 2010), and as we discuss in this review, interactions between these different pathogens, and thus the etiologies of pneumonic forms of pasteurellosis, are often complex and poorly understood (Besser et al. 2013).

Pasteurellosis in wild ungulates

Pasteurellosis has been documented in a range of wild ungulate species other than saigas, with

cases including both hemorrhagic septicemia and pneumonic pasteurellosis (Tables 1, 2). Additional information on the characteristics of these cases is given in Appendix S2i, ii. Generally, the cases concern temperate climates. Although HS is common among domestic ungulates in the tropics, documented cases in wildlife are rare, involve small numbers, and are often closely associated with outbreaks in livestock (De Alwis 1982). We only found one published description of HS in free-ranging wild ungulates in tropical regions (Chandranaik et al. 2015). Among reindeer, most sources describe septicemia, but a bronchopneumonia presentation also occurs (such as in the examples from 1956 and 1973). These are listed in Table 1 under HS rather than under PP as the only pathogen identified was *P. multocida*; however, the etiology of these cases is likely to differ from the others (see Tryland and Kutz 2018 for an overview). Concerning pneumonic pasteurellosis, a disproportionate number of cases have been recorded in bighorn sheep, a highly researched flagship species in which the disease is a major population-limiting factor. There is no documentation of this disease in wild ungulates living in tropical regions. There is some evidence that reindeer do also suffer pneumonic disease associated with *Mannheimia haemolytica* and *Mycoplasma ovipneumoniae* (Mørk et al. 2014), but no detailed case information was available.

In saigas, the number of recorded cases of mass mortality attributed to pasteurellosis is small, and all are listed in Table 3. In some of these cases, diagnosis remains unconfirmed while in others pasteurellosis is unlikely to be the cause. In those cases reported in the years 1974, 1981, and 2012, pasteurellosis was suggested in the cited sources as the cause of death, but the specific identity of the organism and sufficient pathology data to confirm the syndrome are unavailable. There is reasonable evidence for hemorrhagic septicemia in the massive 1988 event and a possibility of pneumonic pasteurellosis in 1984, associated with the presence of *M. haemolytica*. In 2010 and 2011, *P. multocida* was isolated, but full pathological examinations could not be carried out. The symptoms resembled those of fog fever or bloat caused by ingestion of protein-rich vegetation, a hypothesis supported by the association of mortality with a

particular pasture location in both years (references given in Table 3). More details about these MMEs in saigas and maps of outbreak locations are given in Appendix S1.

In addition to cases with identified syndromes (recorded in Tables 1, 2) and the cases in saiga, a number of mass mortality events in the Mongolian gazelle (*Procapra gutturosa*) have been attributed to unidentified forms of pasteurellosis. The largest of these occurred in 1974, killing 140,000 animals, or 35% of the Mongolian population at the time (Dash and Sokolov 1986, Lushchenkina et al. 1988). These cases are discussed in detail in Appendix S2iii.

Much of the literature on hemorrhagic septicemia concerns semi-wild or farmed ungulates such as fallow deer or partially managed boar, living under conditions fundamentally different from those of wild animals (Jones and Hussaini 1982, Carrigan et al. 1991, Eriksen et al. 1999, Risco et al. 2013). The reindeer examples are also from partially managed populations. In addition to the detailed case studies listed in the tables, the Russian literature on HS in Cervidae also appears to focus on farmed animals (Lunitsyn and Bakulov 1985, Lunitsyn et al. 2007, Lunitsyn and Borisov 2012). This may be related to the crowded and stressful conditions under which farmed animals are kept but could also be an artifact of the ease with which they may be observed and monitored.

Implicated pathogens.—In most of the surveyed cases of hemorrhagic septicemia (and those of bronchopneumonia in reindeer), disease was associated with *P. multocida* alone, with the B3 and 4 serotypes often implicated (Appendix S2i). In saiga, the confirmed case of HS in 2015 and the highly likely case in 1988 were both associated with *P. multocida* capsular type B similar to strains in domestic livestock in Spain and South-East Asia (Orynbayev et al. 2019). Overall, only in the case of HS in gaur (Chandranaik et al. 2015) does there seem to have been another “primary” infection (in this case FMDV), which was spread by livestock and exploited by the opportunistic *Pasteurella* organism. The set of pathogens associated with pneumonic forms of pasteurellosis is far larger and more complex than in cases of HS, including *M. haemolytica* and various strains of *P. multocida* together with viruses and other species of the Pasteurellaceae

Table 1. Cases of hemorrhagic septicemia in wild species of ungulate.

Period of outbreak, by species	Location	Serotype	Population size	Numbers dead (and mortality)	Suggested source/trigger	References
Elk/Red Deer <i>Cervus elaphus</i>						
Winter 1985–1986 and 1986–1987	USA	B:3,4	Total: >7000; affected group 2000–3000	1985–1986: 38 individuals (<1%); 1986– 1987†: 10 individuals (<1%)	1985–1986: rain and wind	Franson and Smith (1988), Wilson et al. (1995)
January–April 1993		B:3,4		105 individuals		Roffe et al. (1993), Wilson et al. (1995)
Farmed or park Fallow deer <i>Dama dama</i>						
Winter: 2 outbreaks, 3 weeks apart	Australia	A:3,4	100	13%	Cold, wet, windy	Carrigan et al. (1991)
5 outbreaks from 1992 to 1996‡	Denmark	B:3,4	1800	101, 56, 36, 26, and 48 individuals; (1.4 –5.8%)		Eriksen et al. (1999); see also Aalbaek et al. (1999)
4 July–4 September 1979	UK	B:3,4	264 animals; sub-herd of 60 bucks affected	22 individuals (36% of bachelor herd)		Jones and Hussaini (1982), Rimler et al. (1987) for serotyping and Wilson et al. (1992) for DNA fingerprinting
Wild and farmed fallow deer July 2010	Germany			67 wild deer carcasses found; 10% of 300 farmed deer died§	Hot weather	Soike et al. (2012)
Farmed axis deer <i>Axis axis</i> 23 April–7 May 1985	Australia		130	8 individuals (6%)		Campbell and Saini (1991)
Reindeer <i>Rangifer tarandus</i>						
Summer 1912, 1913, 1924, 1959	Sweden¶			1959: 600–700 died (70% calves) #	Hot weather	Brandt (1914), Nordkvist and Karlson (1962)
October 1911; Summer 1913, 1914, 2005 , 2010; May 1956, 1973††	Norway		1913: 2650	1913: 275 died (10%), most calves‡‡	Hot weather, parasites, stress	Horne (1915), Kummeneje (1976), Skjenneberg (1957), Mørk et al. (2014)
American bison <i>Bison bison</i>						
1911	USA		171	22 individuals (13%)		Mohler and Eichorn (1912–1913)
March 1922 1965–1967	USA	B:3,4	480	3 calves 1 yearling (<1%)§§		Gochenour (1924) Heddlestone et al. (1967), see Rimler and Wilson (1994) for serotyping
Semi-wild boar <i>Sus scrofa</i> September 2010 (6 d)	Spain	B		23 individuals (11%)	Heavy rain	Risco et al. (2013)

(Table 1. Continued.)

Period of outbreak, by species	Location	Serotype	Population size	Numbers dead (and mortality)	Suggested source/trigger	References
Gaur <i>Bos gaurus</i> ^{¶¶} 2013–2014	India	B	Unknown	At least 2 (probably more)	FMDV infection	Chandranaik et al. (2015)

† 81 animals died during winter, ten of these were positively attributed to HS but carcasses were in poor condition.

‡ Some red and sika deer also died.

§ 10–22% of livestock on local farms also died. Deer were considered to be the source of the infection. Another outbreak in Germany 2014 affected livestock and one wild boar (Völker et al. 2014).

¶ *Pasteurella multocida* identified in 1959 Swedish and 1956 and 1973 Norwegian cases; also in 2005 and 2010 cases serotype unknown.

1912: 1600 individuals died of which 80–90% were calves; 1913: 1500 died of which 95% calves; 1924: 1300 of which majority were calves.

|| 1911 and 2005 cases are not fully documented but seem highly likely to have involved a pasteurellosis syndrome (Anonymous 1913, Jystad 2005).

†† 1973 and 1956 cases were diagnosed as bronchopneumonia. While like HS cases the only identified pathogen was *P. multocida*, the etiology of these cases is likely to be different to those of HS.

‡‡ 1911: 850 calves/yearlings; 1914: 25 individuals; 1956: 50 of group of 90 yearlings (in poor condition and infected with parasites); 1973: unknown; 2005: >60 calves; 2010: 44 calves

§§ An additional eight animals were also sick but recovered after antibiotic treatments.

¶¶ At least 30 chitals, 12 sambars, five blackbucks, and seven nilgais also died and were tested positive for FMDV. It is unclear whether the other species also exhibited HS symptoms.

family. There is some evidence that in many of these cases, the primary pathogen may be the bacterium *Mycoplasma ovipneumoniae*. The question of the relative importance of different organisms in pathogenesis has been explored in detail in bighorn sheep (see Appendix S2i). In saigas, while an organism described as *P. haemolytica* was isolated in the 1984 outbreak (Aikimbaev et al. 1985), it is not clear whether other pathogens were not involved or not detected. Antibodies to Parainfluenza-3 virus have been found in Mongolian saiga, so non-detection appears plausible (Enkhtuvshin et al. 2010). One of the pasteurellosis cases in Mongolian gazelles has also been associated with a viral infection (Dash and Sokolov 1986; see Appendix S2iii). Infection with macroparasites may also play a role in susceptibility to disease. Examples include the case of PP in chamois infected with worms *Strongyloides* sp., *Haemonchus* sp. & *Coccidia* (Posautz et al. 2014) and the two cases of bronchopneumonia in reindeer (listed in Table 1) infected with *Hypoderma tarandi*, *Dictyocaulus viviparus*, or *Cephenomyia trompe* (Skjenneberg 1957, Kummeneje 1976).

Mortality rates.—It is apparent from Table 1 that total mortality rates in the majority of reviewed HS cases in free-ranging or farmed species of wild ungulate are low and constitute a small fraction of those observed in saiga (Table 3). Single herds or small populations tend to be affected, so absolute numbers dead are also

low. By contrast, in both the confirmed (2015) and highly likely (1988) cases of HS in saiga, over 200,000 animals died. The only recorded case in wild ungulates involving over 1000 deaths and high mortality rates affected Swedish reindeer (Nordkvist and Karlson 1962). However, all reindeer cases involved predominantly calves, while in saigas adults died first, with calves subsequently dying of starvation or infection through milk. Of the other reviewed cases, there is no particular pattern, with young animals disproportionately affected in some cases, and all age groups equally affected in others. In the cases of pneumonic pasteurellosis listed in Table 2, overall mortality rates in affected herds tend to be high, but disease is typically limited to single herds so absolute numbers of deaths are low. Outside the saiga cases, only Mongolian gazelle mortalities are consistently counted in the many thousands of animals (Appendix S2iii). Moreover, outbreaks of both PP and HS in other species tend to be far more restricted spatially than to those in saiga. Appendix S2ii provides a detailed discussion of spatial and temporal characteristics of outbreaks while Appendix S2iv presents literature on mortality patterns in domestic animals for comparison.

A number of studies, including some of those listed in Tables 1, 2, investigated prevalence in healthy animals and mechanisms of carriage and latency (Appendix S2v). In the saiga examples,

Table 2. Cases of pneumonic pasteurellosis in wild species of ungulate.

Period of outbreak, by species	Location	Isolated pathogens	Popn. size	Numbers dead (mortality)	Suggested source/trigger	References
Bighorn sheep (<i>Ovis canadensis</i>)						
Winter 1995–1996	USA (Idaho, Oregon, Washington)	<i>P. m. multocida</i> a & b & biotype U ⁶ & <i>gallicida</i> ; <i>Bibersteinia trehalosi</i> ; <i>M. haemolytica</i> †; <i>Mycoplasma ovipneumoniae</i> ; parainfluenza 3 virus (PV3)	4 herds	50–75%	Stress during rut may play role.	Cassirer et al. (1996), Rudolph et al. (2007), Weiser et al. (2003)
Winter 1997–2000	USA (Colorado)	<i>M. haemolytica</i> 1 ^G + <i>B. trehalosi</i> ; <i>P. multocida multocida</i> b; <i>E. coli</i> ; <i>Pseudomonas fluorescens</i>	72	28%	Organism of domestic sheep origin	George et al. (2008)
Winter 1990	USA (Wyoming)	<i>P. haemolytica</i> + <i>Moraxella</i> spp; respiratory syncytial virus (RSV); PV3, chlamydia‡	600–900	25%	Selenium deficiency	Ryder et al. (1994), Hnilicka et al. (2002)
Winter 1985–1966	USA (Alberta)	<i>P. haemolytica</i> type A + type T§		60–65 (35–40%)¶	Disturbance; nutritional stress	Festa-Bianchet (1988)
Winter 1986–1987	USA (Oregon)	<i>P. haemolytica</i> ; <i>P. multocida</i> # + PV3; RSV	100	67%	Contact with domestic sheep; rut	Coggins (1988)
Winter 2007–2008	USA (Colorado)	<i>M. haemolytica</i> ; <i>B. trehalosi</i> + <i>P. multocida</i> ; <i>M. ovipneumoniae</i> ; PV3; RSV	21	>30%	At least one organism possibly of livestock origin; severe winter	Wolfe et al. (2010)
Oct-Feb 1980–1981	USA (Colorado)	<i>P. multocida</i> ; <i>Corynebacterium pyogenes</i> ; <i>Prostrongylus stilesi</i>	80	75–85%††	Stress: traffic, dust; noise and harassment and lungworm	Spraker et al. (1984)
Ranch-raised American Bison <i>Bison bison</i>						
December 1996	USA (N. Dakota)	<i>P. haemolytica</i> + <i>P. multocida</i> ; <i>Trueperella pyogenes</i> ; <i>Pseudomonas aeruginosa</i>	20 calves	4 (25%)	Transport of calves in cold temperatures	Dyer and Ward (1998)
Muskox <i>Ovibos moschatus</i>						
August/September 2006	Norway	<i>M. haemolytica</i> + <i>P. multocida multocida</i>	276	71 (25%)	Warm humid weather	Ytrehus et al. (2008)
Chamois <i>Rupicapra rupicapra</i>						
Spring 2010	Austria	<i>M. glucosida</i> : <i>B. trehalosi</i> + Parasites (<i>Strongyloides</i> sp., <i>Haemonchus</i> sp. & Coccidia)		30% all ages	Possibly exacerbated by parasite infestation (animals emaciated)	Posautz et al. (2014)

† Multiple strains.

‡ Prevalence of organisms was similar before and after outbreak, not all may be linked to disease.

§ Probably *Pasteurella haemolytica* & *Bibersteinia trehalosi*. Some animals from which these organisms were recovered did not show clinical signs of pneumonia.

¶ Affected all sex/age groups; did not show the bias to older males often noted in pneumonia outbreaks among bighorns.

Prevalence not given for samples taken during the outbreak; nasal swabs taken from 20 captured adults one year after die-off indicated that 72% were *P. multocida* carriers; *P. haemolytica* detected in only one sample.

|| All rams over 4 yr plus lambs. Animals treated with antibiotics in mid-December.

†† 100% lambs during following summer; 67% following two summers.

the sudden simultaneous death of large numbers of animals of all age groups would seem to imply high background prevalence rates of the pathogen combined with an environmental trigger—and indeed the organism has been detected at high frequencies in the tonsils of animals which died of other causes (Kock 2017). Some studies on cattle and buffalo, in which prevalence has been studied most intensively, suggest relatively low rates of prevalence in healthy animals, high levels during outbreaks followed by a slow decline afterward, and disproportionate mortality among younger animals with lower immunity (see references in Appendix S2v). This would suggest a strong role for transmission of virulent forms of the pathogen in these cases. However, understanding of latency has changed over time and conclusions are hampered by sampling issues. Carriage in the nasopharynx, the most commonly sampled site, is likely to be more transient than that in the tonsillar crypt, retropharyngeal lymph nodes, or other organs where the organism is now known to be latent (De Alwis 1993). It is difficult to obtain uncontaminated samples from sites such as tonsils in a consistent manner, especially from live individuals. The highly variable rates of prevalence recorded in the surveyed literature may reflect these issues, and better methodologies are needed to explore commensalism with this bacterial family.

Below, we look at the roles of environmental factors and transmission between and within species in more detail.

Environmental factors implicated in pasteurellosis outbreaks

Because the organisms involved are commensals, and some cases involve sudden onset in multiple individuals, environmental factors are often implicated in die-offs. Triggers which have been linked to pasteurellosis (of all kinds) include stress due to disturbance, handling, or transport (Spraker et al. 1984, Dyer and Ward 1998, Lunitsyn et al. 2007, Rudolph et al. 2007), and some forms of PP in livestock are referred to as shipping fever for this reason. Intense physical activity such as flight from predators has also been suggested as a trigger (Statsenko 1980), and there is experimental evidence linking stressful exercise with immunosuppression and susceptibility to pneumonic pasteurellosis (Anderson

et al. 1991). More commonly suggested stressors include climate, poor nutrition, or high parasite loads; and deficiencies in certain dietary trace elements or toxic levels of others. A second class of possible causal factor involves the presence of pathogenic strains of the Pasteurellaceae organism in other species (such as domestic ungulates), followed by transmission of these virulent forms to naive populations of wild ungulate. Enhanced intra-specific transmission caused by seasonal aggregation or presence of parasitic vectors has also been posited. The evidence for the influence of the most commonly suggested environmental factors in HS and PP outbreaks is presented with references in Table 4 and summarized here, while more detailed discussion of each is provided in Appendix S3.

Climatic factors.—Association of HS with high humidity, combined with temperatures over a certain threshold, appears to be well established. Climate has also been implicated in forms of pneumonic pasteurellosis such as bovine respiratory disease (BRD). However, the etiology and epidemiology of BRD are different from that of HS and climate may operate through different mechanisms, including viral activity (Taylor et al. 2010). The evidence cited in Table 4 suggests a direct role for climatic factors in pathogenicity, but such factors also affect pathogen survival in the environment, which may be relevant where transmission between individuals is important (see Appendix S3i).

Nutritional factors.—Nutritional stress may cause host immunosuppression, particularly at the energetically demanding periods of gestation and lactation during which HS events in saigas occurred (Houdjik et al. 2001). In most cases considered here, animals were in good condition, (exceptions being cases involving heavy parasite infestations), but this does not rule out deficiencies in labile protein (Appendix S3ii).

Trace elements.—A role for trace elements in susceptibility to pasteurellosis has been suggested through the impact of selenium or copper deficiency on the immune response and iron availability on virulence of *P. multocida*. However, convincing links between trace element levels and disease are difficult to demonstrate in actual outbreaks (Appendix S3iii).

Between-species transmission.—Highly virulent Pasteurellaceae organisms or co-infecting

Table 3. A summary of die-off events in saigas attributed in the listed sources to Pasteurellaceae-related syndromes or in which Pasteurellaceae organisms were isolated†.

Syndrome/ organism isolated‡	Population	Mortality dates	Calving dates	Deaths	% Female	Mortality as % of regional population§	Source
Hemorrhagic septicemia <i>P. multocida</i> [<i>C. perfringens</i>]	Betpak-dala	9–29 May 2015¶	6–24 May	~210,000	96%	~88%	Authors own field notes; CMS (2015), Kock et al. (2018)
Pasteurellosis; probably hemorrhagic septicemia <i>P. multocida</i>	Betpak-dala	12–22 May 1988	Started before 12 May	270,000	97%	75%	Institute of Zoology and Betpak-dala State Hunting Organisation (1988, 1989), Turgai Regional Executive Committee (1988)
Pasteurellosis; possibly pneumonic form <i>P. haemolytica</i>	Ural	February– April 1984	May	110,000	62%	73%	Institute of Zoology and Department of Reserves and Hunting (1984, 1985)
Pasteurella given as official cause, but no detail on syndrome or organism	Betpak-dala	15–16 June 1974	May	1000		<1%	Statsenko (1980)
	Betpak-dala	24–28 May 1981	Mid-May	70,000		15%	Institute of Zoology and Department of Reserves and Hunting (1981, 1982)
	Betpak-dala	17–30 May 2012	9–14 May	>1000	98%	<1%	Dieterich (2012) and Zuther (2012)
Symptoms resemble bloat or fog fever [<i>P. multocida</i>] [<i>C. perfringens</i>]	Ural	18–29 May 2010	1–13 May	12,000		75%	Kock (2011), Kock et al. (2014) and Orynbayev et al. (2013)
	Ural	26–27 May 2011	18–19 May	400		<10%	

† The evidence for confirmation of the syndrome hemorrhagic septicemia and causal organism *P. multocida* is definitive only for the 2015 event.

‡ Organisms in square brackets are those which were isolated from dead animals but which may not be implicated in disease or death.

§ Betpak-dala, Ural, or Ustiurt.

¶ Across all sites. At individual sites, deaths lasted between 6 and 10 d.

pathogens implicated in outbreaks may originate in other species, in which cases transmission from a reservoir species could be a key stage of outbreak etiology. Such a mechanism is suggested in some of the reviewed literature, yet transmission does not always occur, even when it would be expected: In a case where multiple species of deer were kept in the same paddock, only one species was affected (Campbell and Saini 1991). Despite evidence for a high prevalence of *P. multocida* in the saiga environment (Appendix S3iv), relationships between other

potential carriers and saiga outbreaks have not been established.

Intra-species transmission.—There is evidence that differences in seasonal contact rates or exposure to sick animals or carcasses played a role in some of our reviewed outbreaks. Climatic conditions favoring vectors either of the commensal or co-pathogen (such as ticks and flies), although recorded in some commensal-related MMEs (Munson et al. 2008), have not been convincingly demonstrated in pasteurellosis cases. In saigas, HS die-offs have always occurred in dense

Table 4. Evidence for the influence of environmental triggers and transmission in pasteurellosis outbreaks from the reviewed case studies and the broader literature (see Appendix S3 for details).

Factor	Evidence from field studies		
	Hemorrhagic septicemia	Pneumonic pasteurellosis	Evidence from laboratory experiments (all syndromes and organisms)
Climate	Four studies (on bovine livestock, pigs, saiga, and farmed deer species) suggest statistical links between temperature and humidity, and outbreaks (Lunitsyn and Bakulov 1985, Dutta et al. 1990, Gao et al. 2016, Kock et al. 2018). Saiga and Mongolian gazelle cases occur at period of peak precipitation in their respective countries. Five reviewed wildlife cases present anecdotal evidence of unusually hot or cold conditions during outbreak (Table 1) with consistent emphasis on hot summers in reindeer HS cases	Statistical studies on domestic livestock relate morbidity to cold temperatures and high-temperature variability (MacVean et al. 1986, Cusack et al. 2007). Several case studies implicated hot and humid or unusually cold weather in outbreaks (Table 1). One case in saiga occurred during the winter, in contrast with HS cases in that species. Bighorn deaths usually occur in winter months, in particular among males, while calves are more affected in summer	Role of atmospheric conditions in susceptibility to infection has been demonstrated for <i>M. haemolytica</i> (Jones and Webster 1984, Jones 1987, Woldehiwet and Rowan 1988). No studies on <i>P. multocida</i>
Nutrition	No evidence that this is important in HS cases, but outbreaks in saiga and Mongolian gazelles coincide with peak nutritional demand associated with calving and/or lactation.	Nutritional stress has been linked to bighorn lambing rates and lamb survival following die-offs (Enk et al. 2001) and may be associated with individual outbreaks (Festa-Bianchet 1988). Only in the reviewed case involving chamois were animals clearly in very poor condition, due to heavy parasite loads (Posautz et al. 2014)	None
Trace elements	One study on “pasteurellosis” in Mongolian gazelles found trace element levels to be different in die-off areas than on neighboring pastures, but nature of syndrome and pathogen is unconfirmed (Rotshild et al. 1988)	Selenium deficiency linked to low lamb survival following a pneumonic pasteurellosis die-off in bighorn sheep and poor immune competence may have been behind the initial outbreak (Hnilicka et al. 2002)	Virulence of <i>M. haemolytica</i> and <i>P. multocida</i> increased by iron compounds (Mohamed and Abdelsalam 2008, Wilson and Ho 2013). Unbalanced Cu: Mo ratios and low selenium linked to disease caused by <i>M. haemolytica</i> (Stabel et al. 1989, Gengelbach et al. 1997)
Transmission between species	Synchronicity between outbreaks in deer and livestock has been noted on Russian deer farms (Lunitsyn et al. 2007). Two examined cases involved multiple species of deer (Eriksen et al. 1999) or transmission from deer and livestock (Soike et al. 2012). Rodents believed to be source of disease in former Soviet Union (Bakunina 1961, Gordienko and Kovtun 1967)	Cases of PP in bighorn sheep are believed to originate in domestic sheep (Coggins 1988, Wolfe et al. 2010), leading to all-age outbreaks in naïve populations with very high mortality (Cassirer et al. 2013)	None
Transmission between individuals	Epidemiology suggests spread of disease through contact in some HS cases (Brandt 1914, Eriksen et al. 1999) and in reindeer bronchopneumonia (Kummeneje 1976) <i>P. multocida</i> can be carried by parasitic arthropods (Quan et al. 1986); vector-borne transmission suggested (Kummeneje 1976, Dzhupina and Kolosov 1992) but remains undemonstrated	There is evidence that in non-naïve populations, subsequent outbreaks restricted to adults or to calves alone are related to geographical mobility and contact rates (Cassirer et al. 2013). This contact is seasonal and so may have been confounded with climatic factors	None

(Table 4. Continued.)

Factor	Evidence from field studies		
	Hemorrhagic septicemia	Pneumonic pasteurellosis	Evidence from laboratory experiments (all syndromes and organisms)
Co-infection	One case study found FMDV to be a possible predisposing factor (Chandranaiik et al. 2015). Lung parasites are associated with bronchopneumonia cases in reindeer (Skjenneberg 1957, Kummeneje 1976)	All cases of pneumonic pasteurellosis involve multiple pathogens, but not all are opportunistic commensals. Parasite loads associated with one case (Posautz et al. 2014)	Tick-borne fever increases susceptibility to <i>M. haemolytica</i> cytotoxin (Woldehiwet et al. 1993)

Note: Mongolian gazelle cases listed under HS but in fact the syndrome is unidentified.

calving aggregations, yet the rapidity and synchrony of mortality at distant locations and the presence of dead animals outside aggregations suggest a different etiology.

Mortality events caused by other opportunistic bacteria—in ungulates and beyond

Outbreaks in ungulates caused by the other organisms reviewed here follow a similar pattern to most *Pasteurellosis* outbreaks, with relatively low mortality and/or small numbers of animals affected (see Appendix S4 for details). Outside ungulates, *Pasteurellosis* cases in wildlife comparable in magnitude to that of saiga MMEs include outbreaks caused by *P. multocida* in waterfowl, which may cause deaths in the tens of thousands (Friend 1981), but mortality rates do not approach 100% and much smaller outbreaks also regularly occur (Samuel et al. 2004). The syndrome, avian cholera, is caused by a different serotype of *P. multocida* and is generally considered to be an epizootic disease transmitted between individuals rather than the opportunistic response of a pathogen to an environmental trigger. As such, research has tended to focus on survival and transmission of virulent strains in wetland environments (Bredy and Botzler 1989, Samuel et al. 2004, Blanchong et al. 2006). The ungulate commensal *E. rhusiopathiae* has also been shown to cause very high mortality in migratory birds and may now be emerging as an important pathogen in arctic ungulate species (Appendix S4).

The broader literature on commensals suggests a mechanism through which exceptional combinations of climatic factors may cause extreme mortality events. Laboratory studies on abalone (*Haliotis cracherodii*) have demonstrated that large

intertidal temperature ranges facilitate high rates of asymptomatic infection by an intracellular bacterium associated with rickettsial disease. Symptoms are then triggered by subsequent periods of high temperatures (Ben-Horn et al. 2013). This lag between infection and disease expression can lead to sudden and extremely high rates of mortality in the wild, which are not mitigated by the reduction in host density which would usually slow the spread of disease epidemics. Conditions favoring colonization or infection by the initially harmless pathogen are separate in time from those triggering disease and death. Such physiological mechanisms may be common in ectotherms such as amphibians, whose internal temperature is close to that of the environment (Rohr et al. 2013) but are likely to be rarer in mammals.

DISCUSSION

We started this review by asking whether the 2015 mortality event in saiga was unprecedented. We found that the only HS case of similar magnitude in wild or domestic ungulates was also recorded in saigas (in 1988). Hemorrhagic septicemia outbreaks recorded in other wild ungulates bear little resemblance to these events. Often restricted to single herds and a limited spatial range, both the numbers dead and mortality rates tend to be low, even in dense populations. The fact that many recorded cases of HS in wild ungulate species occurred in managed or farmed populations may reflect stressful living conditions or the fact that these animals are closely monitored. It is possible that many cases in wild populations go unnoticed (Preece et al. 2017), but it is unlikely that events on the scale of those

observed in saiga would be undetected, although large die-offs among caribou and reindeer in the subarctic arboreal forests might be an exception and a 50% reduction in the population of these animals has been noted in the past 20 yr (Russell et al. 2018).

Pneumonic pasteurellosis may virtually wipe out single herds, for example bighorn sheep, but again infections tend to be local and thus absolute numbers dead are generally low. From this point of view, if the 1984 MME in the Ural saiga population was a form of pneumonic pasteurellosis, then it must also be considered to be extremely unusual in its scale. However, as we have seen, it is possible that other unidentified organisms may have been implicated in this event.

Cases of possible pasteurellosis most resembling those in saigas are found in Mongolian gazelles. Although overall mortality was lower, deaths were in the tens of thousands and die-offs repeatedly occurred at a particular season and location, suggesting that a specific set of conditions may trigger the disease. But the documentation of these die-offs is insufficient to confirm the identity of the syndrome or micro-organism responsible.

Mortality from other commensal opportunists in ungulates also tends to be low and geographically restricted. More broadly, of all disease-related mass mortality events in mammals, examples affecting over 10,000 individuals have been recorded in only a handful of cases since the 1950s (Fey et al. 2015). Devastating mass mortality is more often associated with acute epizootic viral diseases such as rinderpest or PPR in ungulates (Preece et al. 2017), or similar morbilliviruses in marine mammals (Di Guardo et al. 2005). These generally involve the introduction of the virus into a naive population, sometime combined with immune suppression by environmental pollutants in marine examples (De Swart et al. 1995). Fungal diseases have been implicated in extremely large MMEs in bats and in amphibians, leading to extinction in some cases (Preece et al. 2017). But very severe MMEs caused by commensal organisms following the action of a stress factor appear to be extremely rare.

Future research

Climatic factors are the most consistently hypothesized trigger in reports of hemorrhagic

septicemia. Although conditions anecdotally associated with cases vary widely, the few studies taking a statistical approach (including our study on saigas; Kock et al. 2018) tend to find associations with warmth and relative humidity. However, in saigas, although climatic conditions in the MME years were unusual, they were not unprecedented (Kock et al. 2018), and there are no obvious differences between the ecology and environment of the four main saiga populations (excluding the Mongolian population) that would explain why one (Betpak-dala) has suffered repeated episodes of HS, another (Ural) is implicated in other Pasteurellaceae-related events, and the other two have apparently not been subject to similar events. A further issue with the climate hypothesis is why conditions led to rapid and total mortality in saiga cases and not in other cases reviewed here. Although relative humidity in particular was very high in 2015 relative to long-term averages at the Kazakh region concerned, the absolute amount of moisture in the atmosphere was probably low compared to typical levels in countries such as India where HS cases in domestic animals have been linked to the monsoon. It is possible that in Kazakhstan, humidity is much higher for short periods in the mornings at ground level than would have been detected by Kock et al. (2018), who used data measured at 2 m above the ground. Also, relative humidity itself is problematic as an indicator of atmospheric moisture because it measures the moisture content of air as a proportion of total possible moisture content. The latter increases exponentially with temperature, meaning that the effects of temperature and atmospheric water content are confounded in many climate-disease studies (Shaman and Kohn 2009). Measures of absolute humidity such as specific humidity and vapor pressure may be more biologically meaningful.

In order to address these questions, statistical comparisons of conditions at calving sites between different saiga populations should be carried out. New data collection at calving sites should include portable ground weather-station data for comparison with remotely sensed indicators and studies should include collection of specific humidity data.

However, statistical associations of outbreaks with specific sets of environmental conditions

cannot prove that these conditions actually led to bacterial proliferation and invasion. In vivo laboratory experiments listed in Table 4 demonstrate the influence of climatic factors on *M. haemolytica* proliferation but no such work has been carried out on *P. multocida*. Experiments using laboratory-grown saiga respiratory epithelial cells could be used to study the effects of changing atmospheric conditions at the mucosal surface on *P. multocida*, going some way to demonstrating such a mechanism.

It is also possible that climatic conditions at time of mortality cannot alone explain such an unprecedented event. Cases involving very high mortality rates in other taxa may involve interactions between *Pasteurella* and other pathogens combined with a specific set of climatic conditions, or an initial set of environmental conditions leading to very high colonization rates, followed by a second climatic trigger causing extreme virulence as we saw in abalone. In saiga, only one pathogen was identified, but all hypotheses would imply that a very large proportion of individuals must have been carrying it just before the outbreak. However, the demonstration of long-term commensalism is difficult as the sampling of tonsillar crypts in live animals is problematic and availability of fresh carcasses is low. A better understanding of the different forms of carriage, both latent and shedding; investigations of saiga tonsil anatomy; and standardization of necropsy and histopathology protocols for long-term monitoring would contribute to improved confidence in prevalence rate monitoring.

There is some evidence from the 2015 outbreak that invasion also occurred through the gut (Kock et al. 2018), a phenomenon also observed in infection studies in ruminants (Abubakar et al. 2016). So a link to forage and vegetation cannot be ruled out. Intake of protein-rich forage may cause ruminal stasis, lowering bile production which normally inhibits the development of *P. multocida* in the gut. There was no evidence for particularly unusual forage conditions in the 2015 event and vegetation composition was very different between die-off sites, but long-term vegetation monitoring and saiga fecal analysis at calving sites could be used to measure baselines of nutritional composition and density for comparison if future MMEs occur.

In this review, we have focused on ungulates, but it is also possible that life history and behavioral factors are more important than taxonomic similarities in explaining the mortality rates, numbers dead, and spatial scale of outbreaks. Both saigas and Mongolian gazelles are temperate migratory species living in large herds ranging over huge areas, for which the nutritionally stressful period of calving or lactation follows a severe winter and coincides with the onset of wet periods.

In some ways, the large outbreaks of avian cholera in migratory birds are more analogous to these cases than are cases in other ungulates; this syndrome also follows a similar progression to that of HS—of acute disease following multiplication and invasion across the respiratory tract. In both HS and avian cholera, the genetic and molecular mechanisms involved in the transition from latency or mild chronic pasteurellosis to acute disease are unknown (Shivachandra et al. 2011, Wilson and Ho 2013). Factors determining initial attachment and invasion of host cells, which would enable improved understanding of how putative triggers actually work (Harper et al. 2006), are a research priority. Although PCR typing studies suggest that strains of *P. multocida* found in saiga are similar to those in many other animals, full-genome sequencing would provide more detailed information. Comparison of RNA in the pathogen from affected and unaffected saiga may help to identify differences in gene expression.

In the end, an explanation for the sudden and catastrophic virulence observed in saigas in 2015 must lie in the genetics and microbiology of the host–pathogen interaction, triggered by changes in the external environment. Molecular studies, in concert with experimental pathology designed to test specific hypotheses concerning trigger factors, backed up by extensive fieldwork and monitoring of animals and conditions at calving sites, may eventually reveal the nature of these interactions.

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