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Pasteurella multocida: from Zoonosis to Cellular Microbiology

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SUMMARY

In a world where most emerging and reemerging infectious diseases are zoonotic in nature and our contacts with both domestic and wild animals abound, there is growing awareness of the potential for human acquisition of animal diseases. Like other *Pasteurellaceae*, *Pasteurella* species are highly prevalent among animal populations, where they are often found as part of the normal microbiota of the oral, nasopharyngeal, and upper respiratory tracts. Many *Pasteurella* species are opportunistic pathogens that can cause endemic disease and are associated increasingly with epizootic outbreaks. Zoonotic transmission to humans usually occurs through animal bites or contact with nasal secretions, with *P. multocida* being the most prevalent isolate observed in human infections. Here we review recent comparative genomics and molecular pathogenesis studies that have advanced our understanding of the multiple virulence mechanisms employed by *Pasteurella* species to establish acute and chronic infections. We also summarize efforts being explored to enhance our ability to rapidly and accurately identify and distinguish among clinical isolates and to control pasteurellosis by improved development of new vaccines and treatment regimens.

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INTRODUCTION

We now live in an era where two-thirds of human infectious diseases and three-quarters of emerging or reemerging infectious diseases are zoonotic in origin, i.e., diseases caused by animal-associated pathogens that can be shared with humans (1–4). Coupled with the globalization of air travel and commerce and the megamobilization of the food and trade industries, the spread of zoonotic diseases poses a threat to global public health and biosecurity (2, 4–10). With this backdrop, there are rising concerns among health care officials, policy makers, and the general public about human acquisition of zoonotic diseases from close encounters with pets and other wild or domestic animals (5, 8, 10–16). Over 60% of U.S. households have at least one pet (17, 18). Although cats and dogs still rank highest in the U.S. pet population (17), the popularity of nontraditional or exotic pets is growing (9, 19–21). Combined with the expanding impact of changes in land usage and other anthropogenic activities affecting wildlife habitats (22) and the associated movement of and exposure to animals and animal products (11, 12, 23, 24), these trends are thought to contribute to the increased risk of transmission of known and novel zoonoses (9, 14, 22–30).

Of the hundreds of bacterial species known to commonly reside in the oral, nasal, and respiratory cavities of animals (31–33), *Pasteurella* species are among the most prevalent commensal and opportunistic pathogens found worldwide in domestic and wild animals (34). Pasteurellosis (symptomatic infection with *Pasteurella*) is a high-impact disease in livestock, according to the World Animal Health Organization (OIE) (www.oie.int). In both animals and humans, *Pasteurella* species, most notably *P. multocida*, are often associated with chronic as well as acute infections that can lead to significant morbidity (manifested as pasteurellosis, pneumonia, atrophic rhinitis, dermonecrosis, cellulitis, abscesses, meningitis, and/or hemorrhagic septicemia [HS]) and mortality, particularly in animals (34–36).

Most likely due to routine prompt prophylactic treatment of animal bite wounds with antibiotics, pasteurellosis is still a relatively uncommon cause of mortality in humans (37, 38), even though deaths due to pasteurellosis have increased in recent years in the United States (Fig. 1). Nevertheless, pasteurellosis is often associated with significant morbidity due to complications resulting from animal bite or scratch wounds or from respiratory exposure (39–46). Roughly 300,000 (1%) annual visits to the emergency rooms in the United States are due to animal bite or scratch wounds (45, 47). *Pasteurella* species are isolated from infections resulting from 50% of dog bites and 75% of cat bites (48–50), and indeed, it has been observed ". . . that seemingly trivial animal bites can result in severe complications and that *P. multocida* is an important cause of infection . . ." (49). Other contact with animals, such as kissing or licking of skin abrasions or mucosal surfaces (eyes, nose, and mouth), can also result in infection with *P. multocida* (20, 38, 51–53). In nearly all reported cases of *P. multocida* infection, evidence of prior animal exposure or contact was indicated.

In this review, we provide an overview of the prevalence and pathogenic potential of *P. multocida*, particularly how it relates to animal infections, human-animal interactions, transmission from animal reservoirs, and subsequent human disease. We also summarize what is currently known about the phylogenetic relationships of *P. multocida* with other members of the *Pasteurellaceae* and the pathogenomics, cellular microbiology, and molecular virulence mechanisms that enable *P. multocida* to cause both acute and chronic disease in animals and humans. Finally, we summarize current antibiotic treatment modalities and efforts toward increasing our options for prevention and control of transmission through animal vaccine development.

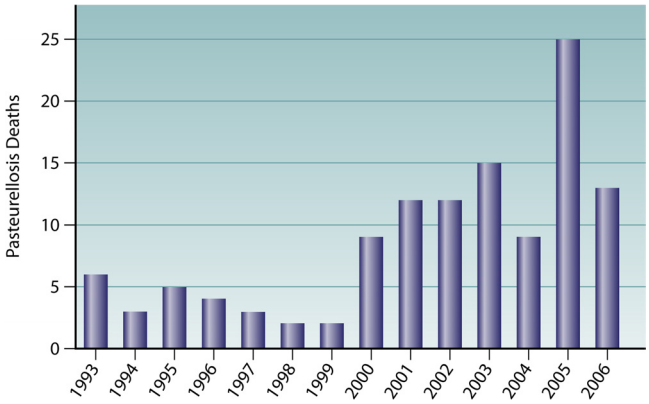

FIG 1 Pasteurellosis deaths in the United States, 1993 to 2006. Data are based on CDC general mortality tables (http://www.cdc.gov/nchs/nvss/mortality_tables.htm).

PASTEURELLA AND THE *PASTEURELLACEAE* FAMILY

Comparative Genomics of the *Pasteurellaceae*

The genus *Pasteurella* is a member of the *Pasteurellaceae* family, which includes a large and diverse group of Gram-negative *Gammaproteobacteria*, whose members are not only human or animal commensals and/or opportunistic pathogens but also outright pathogens (34, 54, 55). Ancestral relationships among bacterial taxa within the *Pasteurellaceae* family can be inferred by comparing their 16S rRNA genes (Fig. 2). Comparative genomic and phylogenetic analyses of the *Pasteurellaceae* have revealed that many members of this highly diverse family were poorly classified (54, 56). Indeed, a number of the *Pasteurellaceae* have already been renamed: *Histophilus somni* (formerly *Haemophilus somnus*, *H. agni*, and *H. ovis*) (57), *Mannheimia* (formerly *Pasteurella*) *haemolytica* (58), *Bibersteinia* (formerly *Pasteurella*) *trehalosi* (59), *Actinobacillus* (formerly *Haemophilus*) *pleuropneumoniae* (60), *Actinobacillus* (formerly *Pasteurella*) *ureae* (61), *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans* (62), *Aggregatibacter aphrophilus* (formerly *Haemophilus aphrophilus* and *H. paraphrophilus*) (62), *Aggregatibacter* (formerly *Haemophilus*) *segnis* (62), *Avibacterium* (formerly *Haemophilus*) *paragallinarum* (63), *Avibacterium* (formerly *Pasteurella*) *gallinarum* (63), *Avibacterium* (formerly *Pasteurella*) *volantium* (63), *Avibacterium* (formerly *Pasteurella*) *avium* (63), *Basfia* (formerly *Mannheimia*) *succiniciproducens* (64), and *Gallibacterium* (formerly *Pasteurella*) *anatis* (65). However, as can been seen from the 16S rRNA phylogenetic tree shown in Fig. 2, further reclassification or renaming may be warranted.

Based on conserved signature sequence insertions and deletions (indels) that are specific for certain subgroups of *Pasteurellaceae* species, it has been proposed that the *Pasteurellaceae* family be divided into at least two clades (66). Two other independent studies produced similar but not identical 2-clade clustering of the *Pasteurellaceae* by using 12 intracellular proteins (67) or 50 conserved proteins (68). However, this attempt to classify the *Pasteu-*

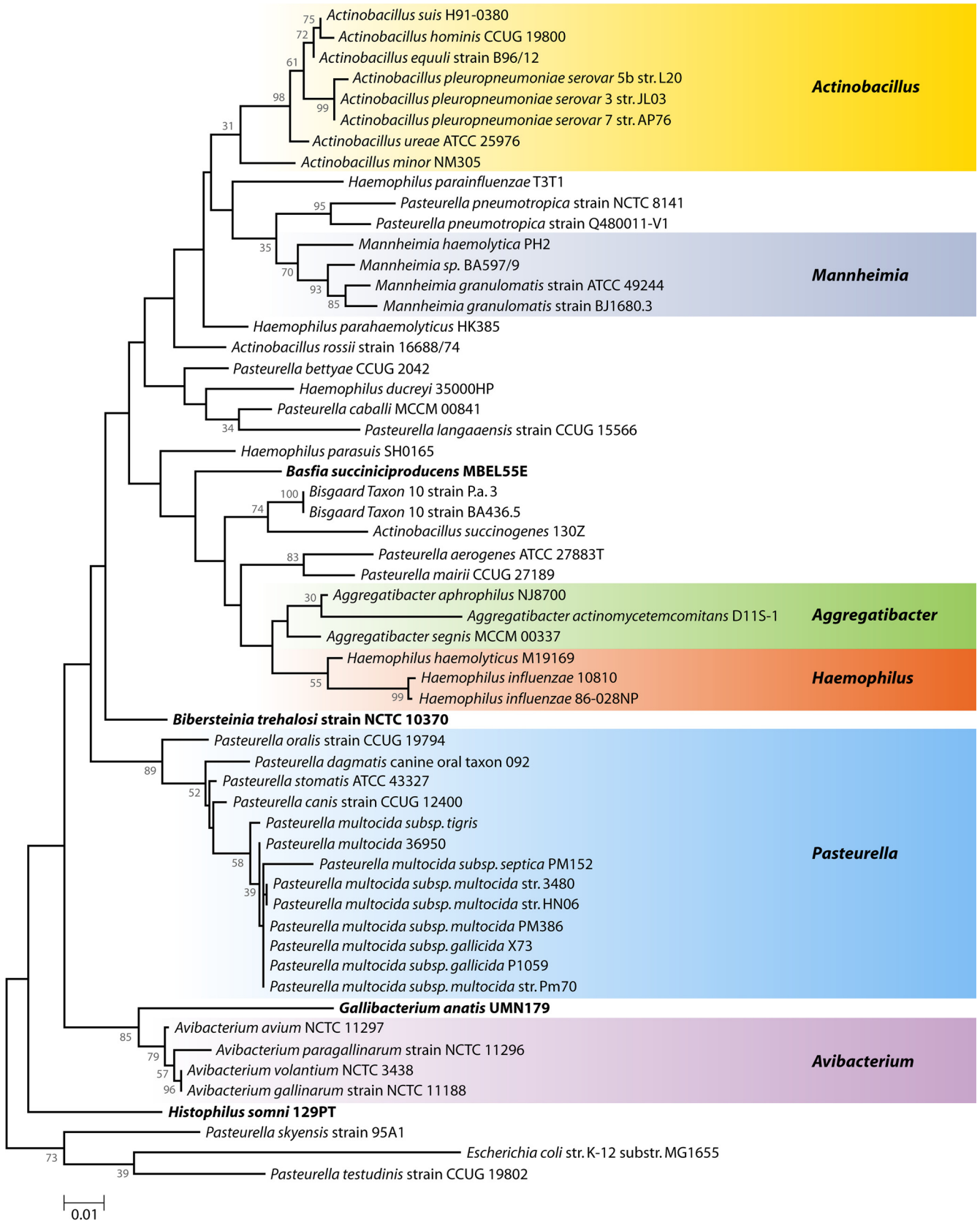

FIG 2 Phylogenetic relationships of *Pasteurella multocida* and related *Pasteurellaceae* bacteria based on 16S rRNA genes. The maximum-likelihood phylogenetic tree was calculated by using MEGA5 (575), based on full-length 16S rRNA gene sequences. Nodes with bootstrap values of greater than 30% after 1,000 replicates are indicated.

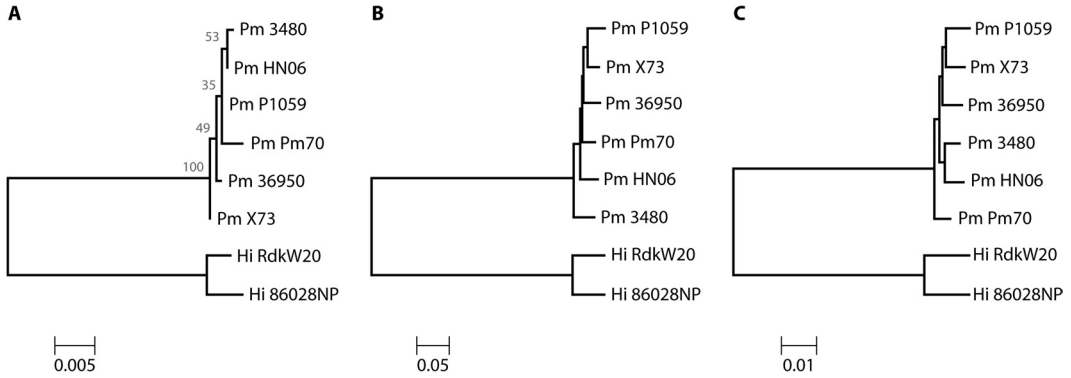

FIG 3 Phylogenetic comparison among selected *Pasteurella multocida* and *Haemophilus influenzae* species with completed genome sequences. (A) Phylogenetic relationships among the strains based on 16S rRNA genes. The maximum-likelihood tree was calculated by using MEGA5 (575), based on the 16S rRNA genes from each of the indicated strains of *P. multocida* (Pm) or *H. influenzae* (Hi) with complete genome sequences. Nodes with bootstrap values of greater than 30% after 1,000 replicates are indicated. (B) Genome-wide comparison based on the fractions of common genes among the strains. The neighbor-joining tree was calculated by using MEGA5 with distances derived from the fraction of genes that are common between each pair of genomes and have >90% coverage in BLASTN alignment. (C) Genome-wide comparison based on the similarity among the common genes among the strains. The neighbor-joining tree was calculated by using MEGA5 with distances derived from the average BLASTN identity for common genes with >90% coverage in alignment.

rellaceae into two clades reflects only the phylogenetic relationships of the genes examined resulting from more recent events such as horizontal gene transfer. Such clustering is not congruent with the phylogenetic tree derived from 16S rRNA gene comparison (as shown in Fig. 2), and it is also not reflective of known host specificities or disease manifestations.

The first *Pasteurellaceae* member to be genome sequenced was *Haemophilus influenzae* strain Rd KW20 (69). Since then, the complete or nearly complete genomes of over 28 members of the *Pasteurellaceae* family have been sequenced, including at least six complete genomes from the species *Pasteurella multocida*. Phylogenetic analysis of 16S rRNA genes alone shows that these six *P. multocida* strains tightly cluster and are distant from *H. influenzae* (Fig. 3A). Genome-wide comparison based on the fractions of common genes (Fig. 3B) or based on similarity among the common genes (Fig. 3C) revealed subtle differences in relatedness among these six *P. multocida* strains. This likely reflects the dynamics of frequent gene transfer events among the pool of *P. multocida* strains. While phylogenetic analysis can readily distinguish *P. multocida* strains from other *Pasteurellaceae*, ancestral relationships among *P. multocida* strains are more difficult to define. Consequently, comprehensive genome-wide comparisons (i.e., pathogenomics) are necessary to account for the extent of diversity observed for pathogenic phenotypes among the *P. multocida* isolates (Table 1).

Pathogenomics of *P. multocida*

A number of genes or gene clusters, identified through signature-tagged transposon mutagenesis (70, 71), *in vivo* expression technology (72), and whole-genome expression profiling (73–75), have been implicated as important for virulence of *P. multocida* (76). Some of these genes encoding putative virulence factors are universally present in all six *P. multocida* genomes, and these include genes encoding outer membrane proteins (*ompA*, *ompH*, and *ompW*), iron acquisition genes (*exbB-exbD-tonB*, *hgbA*, and *fur*), thiamine metabolism genes (*tbpA*, *thiP*, and *thiQ*), and the adhesion/Flp pilus assembly gene cluster (*tadZABCDEFG*). Homologs of the *tad* gene locus are also present in many other *Pasteurellaceae* and Gram-negative bacteria, where they play key roles in biofilm formation, colonization, and pathogenesis (77). Potential virulence genes in *P. multocida* can also be inferred from a list of virulence genes found in the phylogenetically related *H. influenzae* (78).

Unique genes correlated with virulence are present in almost each of the sequenced *P. multocida* genomes. For instance, *P. multocida* strain 36950, isolated from bovine lung, contains the large

TABLE 1 Genome features and phenotypes of sequenced *P. multocida* strains

Strain	Source	Typing	GenBank accession no., size (Mbp)	No. of:	
				Genes	Proteins
P. multocida subsp. *multocida* Pm70	Oviduct of chicken with fowl cholera	Capsular serotype F:3, nontoxinogenic[a]	AE004439.1, 2.26	2,089	2,012
P. multocida subsp. *gallicida* X73	Fowl cholera	Capsular serotype A:1, nontoxinogenic[a]	CM001580.1, 2.27	2,128	2,069
P. multocida subsp. *gallicida* P1059	Turkey liver	Capsular serotype A:3, nontoxinogenic[a]	CM001581.1, 2.31	2,168	2,111
P. multocida 36950	Bovine respiratory infection	Capsular serotype A,[b] nontoxinogenic,[a] ICE*Pmu1*[c]	CP003022.1, 2.35	2,202	2,098
P. multocida 3480	Lung of swine with pneumonia	Capsular serotype A,[b] nontoxinogenic[a]	CP001409.1, 2.38	2,296	2,223
P. multocida subsp. *multocida* HN06	Diseased swine	Capsular serotype D, toxinogenic[a]	CP003313.1, 2.41 (pHN06, 5,360 bp)	2,361	2,265

[a] Based on presence or absence of the *toxA* gene, which encodes PMT.
[b] Based on sequence homology to strains X73 and P1059 within the *cap* locus, which carries genes for capsule biosynthesis (Fig. 4).
[c] ICE*Pmu1*, integrative conjugative element of *P. multocida* (79, 80).

integrative conjugative element (ICE) ICE*Pmu1* of 82 kbp that carries 88 genes, including 12 antimicrobial resistance genes (79, 80). This ICE is not found in any of the other five sequenced genomes; however, a similar ICE was found in *Histophilus somni* 2336 and *Mannheimia haemolytica* PHL213, both of which are bovine respiratory pathogens and thus share the same host niche as *P. multocida* strain 36950. Strain 36950 also has a DNA segment of 9.5 kbp that contains several genes involved in xylose metabolism (*xylA*, *xylF*, *xylG*, *xylH*, and *xylR*). Homologs of this region are present in *P. multocida* strains P1059, P52VAC, HN06, and 3840 but are absent in strains Pm70 and X73.

P. multocida strain Pm70 contains a unique 13.9-kbp region, carrying genes PM1935 to PM1949, that is homologous to a gene cluster found in members of other *Pasteurellaceae* genera, including *H. influenzae* R2846 (13 kbp), *H. somni* 2336 (5 kbp), and *Gallibacterium anatis* UMN179 (5 kbp). However, strain 36950 is the only other strain of *P. multocida* that contains a partial sequence (2.1 kbp) homologous to this gene cluster.

The genome of the toxinogenic *P. multocida* strain HN06 has a unique 18-kbp region carrying 14 genes (PMCN06_2106 to PMCN06_2119), including the *toxA* gene for *P. multocida* toxin (PMT) (the toxin responsible for atrophic rhinitis) and several phage-related genes. A 6.7-kbp segment of this sequence lacking the *toxA* gene is present in the genome of the nontoxinogenic strain 3480. Additionally, there are two regions, a 4.8-kbp region carrying 53 genes (NT08PM_0048 to NT08PM_0100) and a 16-kbp region carrying 22 genes (NT08PM_0622 to NT08PM_0643), in strain 3480 that are also found in strain HN06, albeit fragmented and displaced in multiple loci around the chromosome, further supporting the close relatedness of these two strains. However, there is a 37-kbp fragment (NT08PM_1283 to NT08PM_1334) that is so far unique to strain 3480 and another 33-kbp fragment (PMCN06_1378 to PMCN06_1438) that is so far unique to strain HN06, for which no homologous sequences are found in any of the other strains. It is noteworthy that multiple phage-related genes are present in all of these strain-specific unique sequences, including the segment harboring the *toxA* gene.

Detection, Identification, and Typing of *P. multocida*

Selective culturing and phenotyping of *P. multocida*. Until very recently, conventional methods for detection and diagnosis of infection with *Pasteurella* (pasteurellosis) relied on observation of the bacterium by microscopy using staining and/or isolation by *in vitro* culturing on selective media, followed by phenotypic and/or serological characterization (54). *P. multocida* is a small, pleomorphic, Gram-negative, nonflagellated coccobacillus. Microscopic analysis of fresh cultures or clinical specimens using Leishman's stain, methylene blue, or Giemsa stain shows bipolar-staining rods. *P. multocida* isolates are aerobic or facultative anaerobic and grow well at 37°C on 5% sheep's blood (the preferred culture medium) in dextrose-starch, casein-sucrose-yeast (CSY), chocolate, Mueller-Hinton, or brain heart infusion (BHI) agar (81, 82); however, there is no growth on MacConkey agar. Most clinical isolates are catalase, oxidase, indole, and ornithine decarboxylase positive. Most isolates also ferment sucrose, glucose, and maltose. Media containing vancomycin, clindamycin, gentamicin, neomycin, kanamycin, and/or amikacin, either singly or in combination, have been used to select for *Pasteurella* (83–86), but the results are not always consistent.

Although *P. multocida* grows well on blood agar and chocolate agar, it is easily overgrown by other microbiota in sputum and might be easily misidentified, as it resembles other Gram-negative bacteria such as *Francisella tularensis*, *Yersinia* species, and other *Pasteurellaceae* species (87–89), such as *Haemophilus influenzae* (90) and on first examination even *Neisseria* species (91). Phenotypic characterization of *P. multocida*, based on morphology, carbohydrate fermentation patterns, and serology, is also challenging (92, 93). Identification of *P. multocida* using biochemical strips (such as API 20E/20NE, Minitek, or Oxi/Ferm strips) remains a rapid method commonly used in diagnostic laboratories, but it has limited accuracy (94, 95) and can lead to confusion of *P. multocida* with *Mannheimia* (*Pasteurella*) *haemolytica* (95), *H. influenzae*, or other *Pasteurellaceae* species (90, 96, 97). For example, two reports of identification of *P. gallinarum* as a possible cause of disease in humans were later suspected as possible misidentification as *Haemophilus aphrophilus* due to similarities in phenotype and/or biochemical properties (98). The authors concluded that the API 20NE system does not differentiate among *P. gallinarum*, *H. aphrophilus*, and *A. actinomycetemcomitans*. Most *Haemophilus* species, particularly *H. influenzae*, require chocolate agar or some other source for X and V factors, which *Pasteurella* species do not. However, a number of *Haemophilus* species will grow sufficiently on most blood agar media for growth to be discernible, thus necessitating further differentiation from *Pasteurella* by testing for X and V factor dependency (97). In all, no conclusive diagnostic identification is possible through selective culturing, phenotyping, or direct microscopic examination alone.

Serotyping and ribotyping of *P. multocida*. *P. multocida* isolates are classified based on a combination of capsular polysaccharide serotyping, which distinguishes isolates into one of the five capsular serogroups A (hyaluronic acid) (99), B (arabinose, mannose, and galactose) (100), D (heparin) (101, 102), E (uncharacterized), or F (chondroitin) (101, 102). Isolates are also subtyped based on their lipopolysaccharide (LPS), which separates isolates further into 16 serovars (103, 104). Isolate designations usually consist of a capsular serogroup letter followed by a somatic serovar number (e.g., A:1, A:2, A:3, B:2, etc.). The polysaccharide structure and biosynthetic genes have been determined for three of the capsular serotypes (99, 101, 102, 105, 106), as well as for the LPSs from a number of isolates (103, 107–117).

PCR- plus sequence-based ribotyping analysis using universal primers for 16S rRNA genes, genomics, and other DNA sequence-based molecular techniques have now superseded phenotypic methods for identification, characterization, and differentiation of *P. multocida* and other *Pasteurellaceae* (54, 55, 92, 106, 118–120). Conventional ribotyping based on PCR amplification alone is still generally considered a reliable and discriminative method for characterizing clinical isolates of *P. multocida* (54, 121). However, PCR amplification of 16S rRNA genes, followed by sequencing and sequence comparison against known ribosomal databases, such as the NCBI or the RDP (http://rdp.cme.msu.edu) database, is now the predominant and most reliable method of taxonomically identifying isolates at the genus and species levels.

The availability of additional sequence data for comparing various non-16S rRNA gene clusters has enabled the design of more sophisticated PCR methods for taxonomic identification (16S rRNA gene sequence-based ribotyping) and subtyping (virotyping using non-16S rRNA genes such as those associated with virulence traits) of *P. multocida* isolates (120–122). For example, the *cap* locus has been sequenced for capsule serotypes B:2 (strain

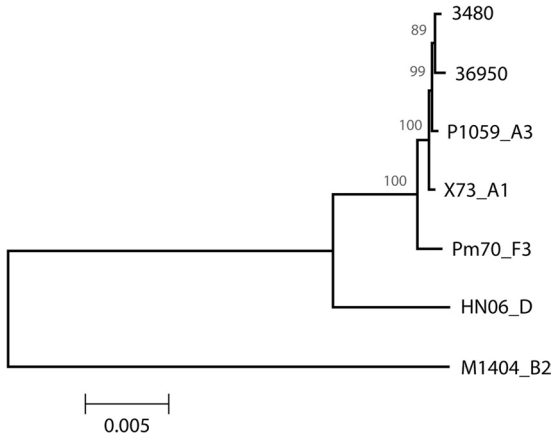

FIG 4 Phylogenetic comparison of the capsule biosynthesis (*cap*) gene locus among selected *Pasteurella multocida* strains. The maximum-likelihood tree was calculated by using MEGA5 (575) with distances derived from genes within the *cap* locus of *P. multocida* serotypes B:2 (strain M1404), A:1 (strain X73), A:3 (strain P1590), and D (strain HN06), as well as the *cap* loci from serotype A strains 3480 and 36950.

M1404), A:1 (strain X73), A:3 (strain P1590), and D (strain HN06) (Fig. 4) and has been used as a basis for serotyping (106, 118). As a consequence, the *cap* loci of previously untyped *P. multocida* strains can now be subtyped based on clustering with the corresponding loci of known serotypes (118, 123–125).

PASTEURELLA DISEASE IN ANIMALS

Pasteurellosis Prevalence

Pasteurella species cause numerous endemic and epizootic diseases of economic importance in a wide range of domestic and wild animals and birds. *P. multocida* is a common commensal or opportunistic pathogen found in the upper respiratory tracts of most livestock, domestic, and wild animals (34), including chickens (126–131), turkeys (132, 133), and other wild birds (123, 134–144), cattle and bison (121, 145–147), swine (34, 148–151), rabbits (152–154), dogs (41, 155–157), cats (domestic house cats as well as large wild cats, such as tigers, leopards, cougars, and lions) (39, 42–46, 49, 157–166), goats (125, 139, 167, 168), chimpanzees (169), marine mammals (seals, sea lions, and walruses) (170), and even komodo dragons (171, 172). The manifestation and pathological symptoms associated with *Pasteurella* infection, or "pasteurellosis," range from asymptomatic or mild chronic upper respiratory inflammation to acute, often fatal, pneumonic and/or disseminated disease.

Transmission is through direct contact with nasal secretions, where a chronic infection ensues in the nasal cavity, paranasal sinuses, middle ears, lacrimal and thoracic ducts of the lymph system, and lungs (173, 174). Preexisting or coinfection with other respiratory pathogens, particularly *Bordetella bronchiseptica* (149, 150, 175–180) or *Mannheimia haemolytica* (147), significantly enhances colonization by *P. multocida*, leading to more severe disease. Interestingly, a recent report showed that *P. multocida* inhibits the growth of *M. haemolytica in vitro* (181). Primary infection with respiratory viruses or with *Mycoplasma* species also predisposes animals to secondary infection with *P. multocida* and/or *M. haemolytica* (176, 182–186). Environmental conditions, stress, and the overall health of the animal also appear to play important roles in disease severity and likelihood of transmission (147, 187, 188).

Pasteurellosis Pneumonia and Atrophic Rhinitis

The predominant syndrome of pasteurellosis in endemic and epizootic infections of wild and domestic animal populations is upper respiratory disease in the form of rhinitis (irritation and inflammation of nasal mucosa and nasal secretions) and lower respiratory disease in the form of pneumonia (in cattle also referred to as bovine respiratory distress syndrome). Symptoms of pasteurellosis in most animals range from mild to severe (44, 178, 189–198). Mild symptoms include sneezing, copious mucous secretions, mild rhinitis, mild pneumonia with labored breathing, and fever but can progress to disseminated disease (hemorrhagic septicemia [further discussed in "Pasteurellosis and Hemorrhagic Septicemia" below]) and/or atrophic rhinitis (atrophy of nasal mucosa, seromucinous glands, and turbinate bones) associated with toxinogenic strains. Pasteurellosis pneumonia without symptoms of atrophic rhinitis is most often caused by nontoxinogenic capsular type A strains of *P. multocida* (147, 151, 199, 200).

P. multocida is often endemic in rabbit colonies and swine herds, where the pneumonia and rhinitis disease is commonly called "snuffles" (148, 154). In more severe cases, symptoms progress toward atrophic rhinitis and, in rare cases, renal impairment, testicular and splenic atrophy, and hepatic necrosis. Atrophic rhinitis in rabbits can also result in overall weight loss, growth retardation, and frequently death. Toxinogenic capsular serotype D and some serotype A strains of *P. multocida* are associated with more severe symptoms of atrophic rhinitis in rabbits and swine (34, 148, 178, 194, 195, 201), with serotype D more prevalent in swine and serotype A more prevalent in rabbits.

The primary overt symptom of atrophic rhinitis in swine and rabbits is twisting or distortion of the snout due to atrophic rhinitis (148, 202–204), manifested as bone resorption characterized by atrophy of the nasal turbinate bones (Fig. 5). Pathological

FIG 5 Atrophic rhinitis in swine. Shown are transverse sections of the nasal cavities of pigs exhibiting pathological symptoms of atrophic rhinitis ranging from mild (left panel) to moderate (middle panel) to severe (right panel) caused by infection with toxinogenic *P. multocida*. (Photos courtesy of the University of Illinois Veterinary Diagnostics Laboratory, Urbana, IL; reproduced with permission.)

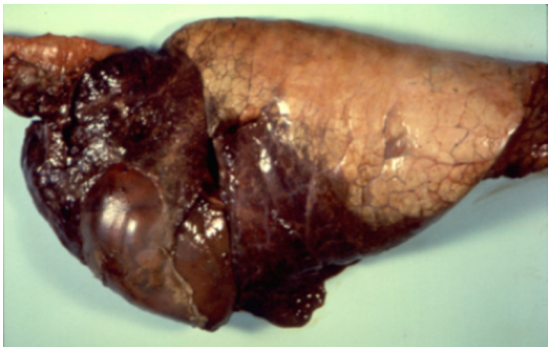

FIG 6 Bovine pasteurellosis bronchopneumonia lung. Shown is an image of a lung lobe from a calf exhibiting pathological symptoms of bronchopneumonia, including extensive hemorrhagic lesions (dark areas), caused by infection with *P. multocida*. (Courtesy of Peter G. Moisan, Veterinary Diagnostic Laboratory, Kansas State University; reproduced with permission.)

changes may be mild and restricted to the snout with no overt clinical signs other than shrinkage of the ventral turbinates. However, infection can develop into more severe and progressive disease with complete loss of all turbinate bone structures and septum deviation, which often results in twisting, wrinkling, distortion or shortening of the snout, sneezing, snuffling, nasal discharge, and teary eyes (205–207).

Pasteurellosis and Hemorrhagic Septicemia

In cattle and other hoofed animals (ungulates), *P. multocida* causes predominantly respiratory disease. Along with *Mannheimia haemolytica*, *Histophilus somni*, *Mycoplasma bovis*, and *Arcanobacterium pyogenes*, *P. multocida* is implicated as a common pathogen associated with bovine respiratory disease (BRD), or "shipping fever" (nonsepticemic pneumonia) (208, 209). *M. haemolytica* is the most predominant isolate from cases of BRD and is associated with acute fulminating, fibrinopurulent pleuropneumonia with hemorrhage or coagulation necrosis due to intense LPS-induced inflammation and production of a ruminant-specific, pore-forming leukotoxin (208). *P. multocida* serotype A:3 is isolated from about 35% of shipping fever cases in the United States (209), manifesting usually as chronic bovine fibrinopurulent bronchopneumonia and occasionally with fibrinonecrosis (Fig. 6) (147, 208). Hemorrhagic septicemia caused by serotype A strains is only occasionally seen in North America (147, 210, 211); however, the proportion of severe hemorrhagic BRD incidences attributed to *P. multocida*, particularly as coinfection with *M. haemolytica* or other pathogens, appears to be rising (121, 146, 176, 183, 208, 209, 212). External stressors such as poor food supply, close confinement, and wet climate conditions are also thought to enhance transmission through contact with nasal secretions of infected animals or fomites (147).

Hemorrhagic septicemia (HS) is a serious acute, highly fatal, and highly prevalent disease in livestock, especially cattle and buffalo, in tropical regions of the world, including Asia, India, Africa, southern Europe, and the Middle East (93, 147, 210, 211, 213–220). HS is caused primarily by *P. multocida* serotypes B:2 and E:2 and is thought to occur at the later stages of pasteurellosis disease (reviewed in reference 221). HS is observed less commonly in swine, sheep, goats, deer, and elk and then is mostly associated with serotype B:2 strains (214, 221). HS may be asymptomatic or unnoticed until onset of the acute stage, which is characterized by rapid onset (within a few hours) and progression. Symptoms usually begin with fever, lethargy, and edema with copious salivation, lacrimation (teary eyes), and nasal discharge, rapidly followed by respiratory distress, septic shock with widespread hemorrhaging, and death within 1 to 3 days. Antibiotic treatment can be effective at early stages, but since acute clinical signs of sepsis manifest so quickly, mortality is nearly 100% after onset (221).

Despite extensive research, very little is known to date about the virulence factors and mechanisms involved in the transition from mild chronic pasteurellosis to acute severe disseminated disease. Recently, a mouse model of HS caused by *P. multocida* serotype B:2 has been developed (222), which might enable further exploration of the roles of different host immune cells and host factors as well as bacterial factors in dissemination of the bacteria in the host.

Pasteurellosis and Fowl Cholera

P. multocida subsp. *multocida* is the most predominant cause of fowl cholera worldwide in a variety of avian species (34, 134, 223), although *P. multocida* subsp. *septica* and *P. multocida* subsp. *gallicida* are also sometimes isolated (223). Capsular serotype A (mainly A:1, A:3, and A:4) is highly correlated to disease predilection for strains associated with fowl cholera (105, 224–227), although capsular serotypes F and D have also been reported (123, 124, 227, 228). Serotype B:3 is often isolated from avian disease cases that manifest as sinusitis (229, 230) with symptoms of nasal discharge, increased lacrimation, swelling, and inflammation. The respiratory tract appears to be the primary site of infection for fowl cholera (126, 129, 223, 231), but isolation of *P. multocida* subsp. *multocida* from avian salpingitis has also been reported (232).

Fowl cholera tends to be an asymptomatic or mild chronic sinusitis and conjunctivitis (229, 230) or pneumonia-like pasteurellosis, but it can suddenly and rapidly develop into a fatal disseminated disease (223). To date, no single bacterial virulence trait or mechanism has been identified as correlating with observed disease incidence or severity (223, 233), but environmental and host factors appear to contribute to onset and outcome severity.

PASTEURELLA AND OTHER *PASTEURELLACEAE* DISEASES IN HUMANS

Pasteurellosis as a Zoonotic Infection in Humans

Humans acquire *Pasteurella* infection primarily through contact with animals, most usually through animal bites, scratches, licks on skin abrasions, or contact with mucous secretions derived from pets (19, 20, 36, 40–42, 46, 48, 90, 158, 160, 163, 165, 185, 234–244). The prevalence of antisera to *P. multocida* was 2-fold higher in healthy individuals with occupational or pet exposure than in a control group with no reported exposure (245), indicating that animal exposure increases the likelihood of subclinical carriage or infection. A survey of the literature over the past 30 years suggests that 20 to 30 human deaths due to pasteurellosis occur annually worldwide, but as mentioned above, this rate appears to be rising (Fig. 1), and in nearly all cases death appears to result as a complication from infection acquired through animal exposure. Among the *Pasteurella* species, *P. multocida* is the predominant human pathogen encountered, especially in severe disease cases (235, 239), although *P. canis* may be more prevalent with dog bites (48, 246–248).

Common symptoms of pasteurellosis in humans from animal bite wounds are swelling (edema), cellulitis (diffuse, localized inflammation with redness and pain), and bloody or suppurative/purulent exudate (drainage) at the wound site (39, 41, 48, 49, 160, 165, 241, 249–255). Leukocyte and neutrophil counts are typically high at the infection site, and inflammation develops very rapidly. In more severe cases, pasteurellosis can rapidly progress to bacteremia (fulminant sepsis) (41, 161, 235, 241, 251, 256–266) and other complications such as osteomyelitis (inflammation of the bone) (155, 165, 267–269), endocarditis (inflammation of the heart) (256, 263, 270–285), and meningitis (inflammation of the meninges) (53, 90, 159, 163, 165, 264, 286–293).

Respiratory infection in humans is relatively uncommon but can occur in patients with chronic pulmonary disease (44, 48, 152, 239, 247, 294–296). In these instances, pasteurellosis can present as severe bilateral consolidating pneumonia and also can cause lymphadenopathy (swelling of the lymph nodes), epiglottitis, and abscess formation (295, 297).

Transmission and Prevalence through Contact with Pets

Infections with *Pasteurella* requiring medical intervention commonly arise as a result of bite or scratch wounds from pets, predominantly cats and dogs (39, 41, 45, 48, 49, 155–157, 161, 240, 242, 243, 249–251, 254, 255, 257, 258, 267, 298–304), but also from other domestic animals (305–308). Bite wound infections with *Pasteurella* tend to be highly aggressive with skin or soft tissue inflammation, erythema, local lymphadenopathy, fever, pain, and swelling often manifesting within 24 h, but they can present as early as 8 to 12 h (41, 48, 159, 166, 309). Pasteurellosis has an overall mortality rate of 25 to 30% among reported human cases of animal bite wounds (38, 90, 163, 288, 289, 310), with bacteremia found in 40 to 63% of all pasteurellosis patients and meningitis plus neurological complications found in 17 to 29% of patients.

Pasteurella infections that do not result from bite wounds are likewise most often associated with *P. multocida* strains (44, 90, 163, 310) and usually involve contact of skin lesions or nasooropharynx or other upper respiratory mucosa with animals or animal secretions, particularly in young children, the elderly, or pregnant or immunocompromised individuals (40, 44, 53, 87, 90, 165, 235, 240, 241, 244, 255, 257, 258, 261, 277, 288, 289, 291, 307, 311–339).

Neonatal meningitis (usually with septicemia) has been reported (90, 91, 288, 313, 340–342), but in nearly all cases the most likely route of transmission was attributed to direct exposure to pets or other domestic animals. Vertical transmission from mother to child was reported rarely (291, 341). Only three instances of human-to-human horizontal transmission have been reported. In two cases transmission was likely from the father, who had exposure to chickens (286) or sheep (343), and in the third case the mother tested negative for *P. multocida* colonization but the grandmother tested positive, as did her pet dog (344).

Patients with underlying diseases that contribute to an immunocompromised condition, such as cirrhosis (liver dysfunction) (39, 43, 241, 244, 249, 255–257, 260, 262, 263, 265, 266, 273, 275–280, 292, 312, 314, 316, 317, 321, 322, 328, 329, 335, 337, 345–359), renal failure (kidney dysfunction requiring dialysis or indwelling catheters) (253, 267, 300, 302, 303, 318, 324, 326, 327, 360–366), or HIV-positive status (especially if taking immunosuppressive drugs or experiencing other disease conditions) (290, 310, 315, 367–369), have an increased risk of peritonitis, endocarditis, and/or septicemia caused by *P. multocida*. This is particularly the case if there is a history of exposure to pets. Indeed, in almost all of the above-mentioned reports, the authors caution patients with these conditions about the risks associated with exposure to pets and/or alert clinicians to consider possible complications with *P. multocida* infection for cases with pet ownership or a history of animal exposure.

It is noteworthy that in human infection cases the subspecies or serotype of the *P. multocida* clinical isolate is rarely reported (370). However, there are a few studies where this has been examined retrospectively. In one study, 143 isolates collected from human patients over a 12-year period (1983 to 1994) were biochemically characterized for distribution at the species and subspecies levels as well as capsular groups (239). Most of the isolates were determined to be *P. multocida* subsp. *multocida*, with the remaining being *P. multocida* subsp. *septica*, *P. multocida* subsp. *gallicida*, *P. canis*, *P. dogmatis*, and *P. stomatis*. While *P. multocida* strains were associated with cat and dog bites, *P. canis*, *P. dogmatis*, and *P. stomatis* strains were recovered only from dog bites, and *P. multocida* subsp. *multocida* and *P. multocida* subsp. *septica* were most frequently associated with cat bites. Most of the animal bite isolates were non-group A capsular strains (serogroup D) and were associated more with disseminated disease. Capsular serogroup A strains were associated more with respiratory infections. Similar findings were observed for isolates recovered from infected patients in four other studies involving 159 strains (247), 107 strains (48), 54 strains (294), and 20 strains (296).

Rare Cases of Zoonotic Transmission through Wild Animals

Although zoonotic transmission from wild animals is relatively rare, *Pasteurella* infection is a serious concern in cases of bite wounds from wild animals. Similar to that for bites from their smaller domestic relatives, *Pasteurella* infection is a high risk for bites from large cats, including lions, tigers, cougars, and others (159, 162, 164, 166, 293, 371–375). Cases of *Pasteurella* infections have also been reported for bites or exposure to mucous secretions from other wild and domestic animals, including rats, opossums, horses, and rabbits (166, 259, 287, 295, 376). Although these incidents of severe outcome from zoonotic exposure appear to be relatively uncommon, it has been proposed based on historical precedence that there is a potential threat for any pathogen that exclusively infects animals to evolve into a pathogen that more readily transmits among animals and humans and then converts into a bona fide human-specific pathogen (377). It is not hard to speculate that there is potential for a zoonotic pathogen such as *Pasteurella*, which is highly prevalent in animals and can transmit to humans, to convert into a human pathogen upon acquisition of additional virulence traits.

Human Diseases Caused by Other *Pasteurellaceae*

In contrast to *Pasteurella*, most of the other members of the *Pasteurellaceae* family are primarily animal commensals or enzootic or epizootic pathogens, with a few notable exceptions which are primarily human pathogens. These will be discussed in this section.

Haemophilus. *Haemophilus influenzae* is frequently found as a commensal in healthy adult humans but can cause invasive infections in humans, which present as cellulitis, arthritis, pneumonia, sepsis, or meningitis and can often become life threatening. There

are six identifiable types and some nontypeable strains of *H. influenzae* associated with human disease. *H. influenzae* type b (Hib) is the most prominent form (378). Before introduction of the Hib vaccine, Hib was responsible for about 20,000 cases of and about 1,000 deaths from severe disease in children annually, but invasive Hib disease has nearly been eradicated since the introduction of the Hib conjugate vaccine (379). Other strains of *H. influenzae*, particularly noncapsular (nontypeable) strains, remain important pathogens in humans worldwide (379–381).

H. influenzae biogroup aegyptius is responsible for recurring outbreaks of seasonal acute, purulent conjunctivitis, more commonly known as pink eye (382). In 1984, a new, highly virulent strain emerged in Brazil that caused a highly lethal disseminated disease in young children, called Brazilian purpuric fever (BPF) (382, 383). The infection presented as an acute, purulent conjunctivitis before rapid onset of bacteremia and progression to septic shock, with mortality rates as high as 70% (383). A pan-genomic analysis of the invasive BPF isolate with other noninvasive *H. influenzae* isolates responsible for conjunctivitis identified significant differences in the repertoire of autotransporter adhesins as well as new fimbrial proteins, which were suggested to contribute to virulence through altered host-pathogen interactions (382).

Haemophilus haemolyticus is closely related to *H. influenzae* but is generally considered to be a nonpathogenic human commensal found in the pharynges of some individuals (384). However, *H. haemolyticus* can be mistaken as nontypeable *H. influenzae* due to its lack of a capsule and its variable hemolytic properties on blood agar (384, 385). Cases associated with invasive clinical disease in postsurgical patients have been identified using 16S rRNA sequencing (386).

Haemophilus ducreyi is a strict human pathogen that naturally infects genital and nongenital skin (387), causing genital ulcerative disease known as chancroid (388–390). Interestingly, *H. ducreyi* is more closely related to the animal pathogens *M. haemolytica* and *Actinobacillus pleuropneumoniae* than to other human pathogens of the *Pasteurellaceae* family (Fig. 2) (68). Identification of virulence genes and elucidation of the molecular basis of pathogenesis in *H. ducreyi* may provide insight into how a pathogen could adapt to occupy a unique niche in a human host (390).

Actinobacillus. Most *Actinobacillus* species are enzootic or epizootic pathogens; *A. hominis* and *A. ureae* are the only known exceptions, being highly adapted to humans. Both are relatively uncommon commensals of the human respiratory tract but can cause infections. *A. hominis* can cause lower respiratory tract infections that can progress to bacteremia, sepsis, or meningitis and in severe cases can result in death, particularly in immunocompromised individuals (391). Most cases of *A. ureae* infections are associated with predisposing factors, such as head trauma, a neurosurgical procedure, liver cirrhosis, alcoholism, diabetes, malnutrition, or immunosuppression (392–395). For example, *A. ureae* meningitis was found in a number of immunocompromised patients (392, 394). *A. ureae* has also been associated with bone marrow infection and septic arthritis in a patient with rheumatoid arthritis taking a tumor necrosis factor alpha (TNF-α) inhibitor (395).

Aggregatibacter. *Aggregatibacter actinomycetemcomitans* is a common periodontal pathogen responsible for periodontitis, a chronic inflammatory disease that manifests as loss of supporting connective tissue and alveolar bone around teeth with symptoms of malodor, gingival bleeding, pain, and swelling (396). It is also a major pathogen causing endocarditis (397) and brain abscesses (398). *A. actinomycetemcomitans* produces two toxins as major virulence factors responsible for pathogenesis: a pore-forming leukotoxin (LtxA) that kills white blood cells in gingiva and thereby helps evade the host immune response during infection (399) and a cytolethal distending toxin (Cdt) that enters host cells to cause cell cycle arrest or apoptosis through its DNase activity and thereby causes extensive damage to gingival tissue (400, 401).

Aggregatibacter aphrophilus is also an oral commensal occasionally found in humans that causes bone and joint infections and endocarditis in some cases (402). Its genome contains genes that encode a type VI secretion system (T6SS) as well as several putative T6SS effector proteins that may contribute to virulence (403).

PASTEURELLA VIRULENCE MECHANISMS

Survival in the Host Environment

Extensive research activities, including a number of genome and transcriptome analyses, are beginning to shed light on the virulence mechanisms of *P. multocida* (reviewed in reference 233). Several factors appear to be involved enhancing survival in the host environment: iron acquisition mechanisms that enable *in vivo* growth; membrane lipopolysaccharide (LPS) that confers serum resistance; capsule that prevents phagocytosis; surface components that provide adherence properties; extracellular matrix-degrading enzymes such as hyaluronidase, neuraminidase, and proteases that facilitate colonization and/or dissemination; and in some highly virulent strains a dermonecrotic toxin (PMT) that causes atrophic rhinitis and dermonecrosis and modulates the immune response. This section will explore what is currently known about the role of each of these mechanisms in *P. multocida* pathogenesis.

Nutrient acquisition. During later stages of infection, *Pasteurella* encounters host niches that require changes in gene expression for pathways involved in central energy metabolism and in uptake of various nutrients such as iron and amino acids. Most *P. multocida* genes shown to be upregulated during infection are involved in nutrient acquisition and metabolic processes (404). Highly virulent strains of *P. multocida* often secrete various hydrolytic enzymes that presumably facilitate nutrient acquisition or dissemination. Virulent serotype B strains, particularly serotype B:2 isolates from hemorrhagic septicemia cases, produce a hyaluronidase (405, 406). Production of sialidases (neuraminidases), which scavenge sialic acid from host membrane components and serve to evade host defenses by blocking mucin action, is also prevalent in virulent strains of *P. multocida* (407–410).

Iron acquisition. Iron is an important nutrient for nearly all life forms. Bacterial pathogens, when in a vertebrate host environment, will encounter a depletion of iron, triggering release of the transcriptional control of ferric uptake regulator (Fur), which represses genes under its control in the presence of iron (411). It is possible that iron acquisition in *P. multocida* plays an important role in its survival and pathogenesis in the host, particularly considering that more than 2.5% (53 coding DNA sequences) of the Pm70 genes are predicted to encode proteins homologous to known proteins involved in iron uptake or acquisition (412). Gene expression profiling under iron-limiting conditions have identified several iron acquisition genes at increased expression levels (413), and indeed, different sets of genes appear to be ex-

pressed in response to the nature of the iron source (414). Many iron acquisition-related genes have been predicted to be part of the outer membrane proteome (415). Although iron-dependent expression profiling of the outer membrane proteome still needs to be investigated, most of these membrane proteins were shown to be protective antigens (416).

Some *Pasteurellaceae* species have strict host specificity. Iron acquisition system requirements are considered to be an important restricting factor for host specificity. For example, the porcine pathogen *A. pleuropneumoniae* utilizes porcine transferrin as an iron acquisition vehicle through binding to a bacterial surface receptor, which is comprised of the transferrin-binding proteins TbpA and TbpB. *A. pleuropneumoniae* binds only porcine transferrin and not bovine or human transferrin (417). Similarly, the bovine pathogen *M. haemolytica* has a transferrin-binding receptor that binds only bovine transferrin (417, 418). It has also been reported that most strains of *H. somni* are capable of acquiring iron only from bovine transferrin through binding to the bipartite TbpA-TbpB transferrin receptor, but some strains can also utilize ovine or caprine transferrin through a single-component TbpA2 transferrin receptor (419). Although no TbpA-TbpB homologs are encoded in the six complete genomes of *P. multocida*, they all have genes coding for homologs of the single-component transferrin receptor and other hemoglobulin/transferrin/lactoferrin receptor family proteins. In addition, *P. multocida* strains have siderophore-independent iron acquisition systems homologous to the *Actinobacillus* AfeABCD system (420) and the periplasmic binding protein-dependent iron transport systems homologous to *E. coli* FecBCDE (421), *Neisseria* FbpABC (422), and *Actinobacillus* AfuABC systems (423), which can utilize xenosiderophores for iron acquisition. The presence of multiple iron acquisition systems in *Pasteurella* species may account for their ability to infect multiple hosts.

Surface components. (i) LPS. *P. multocida* lipopolysaccharide (LPS) confers resistance to serum complement and is a major virulence determinant (113, 114, 117, 424). Avian strains with mutations in LPS are highly attenuated in chickens (109, 117). *P. multocida* strains express two LPS glycoforms (A and B) that differ in their inner core structure (114, 117), whereas the outer antigen structure varies among strains and has been classified into 16 different LPS serovars (107, 109). Protection against *P. multocida* infection appears to be serovar specific (108).

(ii) Capsule. *P. multocida* expresses a hydrophilic capsule that inhibits phagocytosis and complement-mediated opsonization (224, 425–427). Loss of capsule biosynthesis results in highly attenuated strains that are no longer serum resistant (105, 224). The major polysaccharide component of serotype A capsule is hyaluronic acid, which is consistent with its structural properties (99) and sensitivity to hyaluronidase (226, 428). The *hexA* gene responsible for capsule export, located in an 11-gene *cap* locus in the *P. multocida* strain X73 (serotype A:1) (226), is required for growth in both chickens and mice (224). The apparent predominance of serotype A strains in zoonotic respiratory carriage and infections in humans (48, 85, 152, 239, 294) has been attributed to the antiphagocytic properties of the mucoid capsular hyaluronic acid components (239, 429), which prevent phagocytic clearing and promote mucosal colonization of the lower respiratory tract in humans.

In contrast to the serotype A capsule, the serotype B polysaccharide capsule consists of arabinose, mannose, and galactose sugar residues with as-yet-unclear linkages (427). The *cexA* gene, a homolog of *hexA*, is part of a 15-gene capsule (*cap*) biosynthesis locus and has been shown to be a virulence determinant for *P. multocida* strain M1404 (serotype B:2) in mice (426). Serotype B and E isolates are infrequently recovered from human infections (239).

Based on sensitivity to mucopolysaccharidases, structural composition analysis, and cloning and sequencing of the capsule biosynthesis genes, serotype D capsules are comprised of heparin or heparin sulfate (101, 102, 430), and serotype F capsules are made of chondroitin (101, 430, 431). The capsule biosynthesis gene loci for serotypes A, D, and F appear to have high similarity with each other but can be distinguished by multiplex PCR-based typing analysis (106, 118). Human clinical isolates with serotype D capsules are most often associated with systemic infections resulting from skin and soft tissue exposure (48, 85, 152, 239, 247, 294, 296).

Although noncapsular variants may arise through mutational events, there is evidence that capsule biosynthesis might be transcriptionally regulated (105). Through study of acapsular strains of *P. multocida*, a single-site mutation in the *fis* gene outside the *cap* locus was found to prevent capsule production despite the strains having an intact biosynthetic locus (432), suggesting that regulation of capsule production is possible through the Fis protein, a known transcriptional regulator in other bacteria.

(iii) OMPs. Putative adhesins that enhance colonization by *P. multocida* have been reported (34, 433–442). OmpA is an outer membrane protein (OMP) that serves as an adhesin by binding to host extracellular matrix proteins, such as fibronectin (437, 438, 443). OmpH is a major outer membrane porin that forms a homotrimeric channel and has shown some potential as a protective antigen (444). OmpH and *Pasteurella* lipoprotein E (PlpE) are protective surface antigens associated with *P. multocida* serotype A:1, A:3, and A:4 strains isolated from cattle with shipping fever (445, 446) and from birds with fowl cholera (416). OmpA and OmpH proteins show considerable heterogeneity, and at least among avian *P. multocida* strains, a number of different variants appear to be associated with certain capsular serotypes (B, D, or F) (200, 227).

Oma87, an 87-kDa outer membrane protein present in all *P. multocida* strains that is expressed *in vivo*, shares sequence similarity with the surface D15 protective surface antigen of *H. influenzae* (447). Another protective surface antigen that has been identified is a 39-kDa adhesion protein (Cp39) present in avian *P. multocida* strains P-1059 (serotype A:3) and X-73 (serotype A:1) (436, 448).

The type IV fimbrial subunit PtfA has been identified and characterized from serotype A, B, D, and F strains (439, 449–451); however, the role of type IV fimbriae in adhesion, host specificity, and colonization is not yet clear. On the other hand, an analogous type IV pilin protein, Tfp, of *Pseudomonas aeruginosa* has been shown to bind lung epithelial cells, leading to pathogenic effects in the host (452).

Growth of *P. multocida* strains under iron-limited versus iron-rich conditions showed iron-dependent changes in iron acquisition genes (413, 414), several of which were identified as encoding OMPs (453). Further insights about the role of these iron acquisition OMPs in the pathogenic potential of *P. multocida* could be gained by more comprehensive outer membrane proteomic analysis of these proteins in response to various iron and nutrient conditions. Despite all these reports and studies showing their potential use as protective antigens for component vaccines (see

below), no OMP has yet been shown to be an essential virulence factor.

(iv) Filamentous hemagglutinin. *P. multocida* possesses two filamentous hemagglutinins, FhaB1 and FhaB2 (also named PfhB1 and PfhB2, respectively) (70, 412). These proteins are similar to the LspA1 and LspA2 filamentous hemagglutinins from *H. ducreyi* (454), mutations of which have been shown to affect virulence (455). A similar filamentous hemagglutinin in *Bordetella pertussis* and *B. bronchiseptica* is required for biofilm formation and colonization of the nose and trachea in mice (456, 457). FhaB2 in *P. multocida* has been implicated in virulence (70, 458), and expression of FhaB2 was found to be reduced by 4-fold in a nonmucoid *P. multocida* variant, AL1114 (432). FhaB and its transporter FhaC form a two-partner secretion system that is similar to the FhaB-FhaC system in *Bordetella* species (456, 459), LspA-LspB in *H. ducreyi* (455), and IbpA-IbpB in the pathogenic *Histophilus somni* strain 2336 (460), which act to inhibit phagocytosis. Genome-wide comparison showed that the IbpA-IbpB system and two other immunoglobulin-binding proteins, p76 and p120, are absent in the avirulent *H. somni* strain PT129 (460).

PMT. Once it was discovered that only certain capsular serotype D and A strains of *P. multocida* were responsible for chronic turbinate atrophy, a large protein toxin was identified, isolated, and cloned from these strains (148, 194, 196, 461, 462). The purified, 146-kDa *P. multocida* toxin (PMT), encoded by the *toxA* gene located on a putative lysogenic bacteriophage (463), was subsequently demonstrated to be the primary agent responsible for the symptoms of atrophic rhinitis (461, 464–471), as well as a number of other clinical symptoms associated with *P. multocida* infection (189, 190, 192, 461, 464, 470, 472–475). PMT-mediated bone atrophy appears to occur through disruption of normal cell signaling processes in bone-generating osteoblasts and macrophage-like osteoclasts (205, 206, 466, 476–482). In humans, toxin-producing strains are often isolated from respiratory carriage or infections (483), but a role for PMT in human pulmonary disease has not yet been established.

PMT is a member of the dermonecrotic toxin family of G-protein-deamidating toxins, whose molecular mechanism of action has been thoroughly reviewed (201, 484–487). Mounting evidence suggests that PMT enters mammalian cells (reviewed in reference 486) and exerts its pathogenic effect on cells through modulation of multiple signaling pathways (reviewed in reference 485). Recent studies have revealed that in addition to the α subunit of the heterotrimeric G_q protein (488–490), PMT also acts on other G proteins, i.e., G_{11}, G_i, and $G_{12/13}$ (488–494). A number of studies have implicated PMT as a modulator of host immunity (475, 495–498) and cellular differentiation and proliferation (476, 477, 485, 499–507). Interestingly, because of its potent mitogenic and proliferative properties, there has been speculation that exposure to PMT might play a role in cancer predisposition as a long-term consequence of infection with toxinogenic *P. multocida* (485, 495, 499, 504, 505, 508–510).

DNA Uptake

A number of the *Pasteurellaceae* are competent for DNA uptake, and two high-frequency uptake signal sequences (USS) have been identified for members of the *Pasteurellaceae* (67): the USS (AAGTGCGGT) found in *P. multocida*, *H. influenzae*, *Aggregatibacter actinomycetemcomitans*, *Histophilus somni*, and *Mannheimia succiniciproducens* and the closely related USS (ACAAGCGGT) found in *Haemophilus ducreyi*, *Actinobacillus pleuropneumoniae*, and *M. haemolytica*. The common USS and conservation of all competence genes among these family members suggest a common ancestral origin of competence.

The mechanism for DNA uptake and organization of the competence apparatus of *P. multocida* can be inferred from the better-characterized *H. influenzae* system (511). All six completed *P. multocida* genomes harbor the entire set of competence-related genes, including *comABCDE*, *comF*, *comEA*, *comEC/rec2*, and *orfJ*. The presence of competence as well as a universal USS favors the ready exchange of virulence traits through horizontal gene transfer among these family members and accounts for many of their similar pathogenic properties. It is interesting that only four family members (*H. somni*, *H. ducreyi*, *M. succiniciproducens*, and *M. haemolytica*) appear to have recently acquired mutations resulting in defective competence systems (67).

Transformation of *P. multocida* usually requires *P. multocida*-specific vectors (512). Most effective transformation methods for genetic manipulation of *P. multocida* involve conjugation using shuttle vectors (513–515) or the use of transposons (70, 516). The capsules of some *P. multocida* strains are known to hinder transformation of nonspecific vectors, but the presence of mucolytic enzymes or coculturing with bacteria producing capsule lytic enzymes has been reported to enhance the competence of capsulated *P. multocida* X73 (513). This finding implies that enhanced competence and acquisition of new virulence genes could occur under various infection conditions, including coinfections or polymicrobial infections.

Antibiotic Resistance

While not all strains of *P. multocida* harbor plasmids, plasmids of various sizes (usually 1 to 6 kb but up to 100 kb) have been identified in isolates from various sources (517). Most of these plasmids confer resistance to various and often multiple antibiotics (517–531), most frequently β-lactams, tetracycline, chloramphenicol, streptomycin, and sulfonamides. In addition to the antibiotic resistance genes, a few of these plasmids have also been found to carry genes with other functions, such as plasmid mobilization, segregation, or replication genes (522) and putative cation transporter genes (80, 532). Many of the plasmids carrying antibiotic resistance determinants are transferrable among the *Pasteurellaceae* members, as well as other Gram-negative bacteria (517, 518, 522, 529, 533–536).

Multiple antibiotic resistance genes have been identified on mobilizable or conjugative elements integrated into the chromosomes of some strains. For example, genes encoding multiple antibiotic resistances have been identified integrated into the chromosome of the genome-sequenced *P. multocida* strain 36950 isolated from a case of BRD that exhibited resistance to all the antibiotics commonly used to control BRD (80, 537). Interestingly, the 85-kb ICE*Pmu1* element carried 88 genes, including 12 different resistance genes that were distributed between two regions of resistance (80), a 15.7-kb region at one end of the element and a 9.8-kb region at the other end. ICE*Pmu1* also contains genes involved in conjugative transfer of the element and its chromosomal excision/integration, genes encoding putative metabolic enzymes involved in alcohol, aldehyde, and ketone catabolism, and genes encoding a lysozyme-like protein and a copper-oxidase-like protein (79). A 5.2-kb mobilizable plasmid, pCCK647, encoding spectinomycin/streptomycin resistance was identified in a

capsular serotype F strain isolated from a case of bovine peritonitis (520).

TREATMENT AND PREVENTION

Antibiotics

Broad-spectrum antibiotics that target *Pasteurella*, as well as other Gram-negative and Gram-positive bacteria, are the preferred prophylaxis for animal bites, which tend to be polymicrobial in nature (32, 41, 48, 309). *Pasteurella* species are not very susceptible to erythromycin, lincosamides (such as clindamycin), or certain β-lactams (such as dicloxacillin or cephalexin), so these antibiotics are not recommended as monovalent treatments for animal bites. Instead, a combination of amoxicillin and the β-lactamase inhibitor clavulanic acid (Augmentin), doxycycline plus metronidazole for patients with penicillin allergies, or clindamycin plus a fluoroquinolone (ciprofloxacin, or trimethoprim-sulfamethoxazole combination for children or ceftriaxone for pregnant women) is the recommended treatment regimen (41, 48, 309).

Vaccination

The relatively low incidence of human pasteurellosis, despite the high prevalence of *Pasteurella* species in domestic and wild animals, supports the premise that *Pasteurella* is an opportunistic pathogen for humans. Further support for this comes from studies examining the carriage and anti-*Pasteurella* antibody levels in individuals with occupational or other extensive exposure to animals (85, 152). Because of the relatively low incidence of human infection, most immunization or vaccination studies against *Pasteurella* infection have been geared toward controlling animal disease. Despite considerable effort and ample experimental animal models, mechanisms of protective immunity against *Pasteurella* remain elusive, and so development and evaluation of effective vaccines have been challenging (34, 449, 538).

Detection of high serum levels of IgG antibodies is not indicative of clearance of or resistance to *Pasteurella* infection but rather is indicative of chronic infection (178, 475, 539, 540). Vaccination using toxin-based component vaccines, bacterins, or live attenuated bacteria is effective against toxin-mediated disease, such as atrophic rhinitis (449, 471, 541–552). A commercial swine vaccine based on *P. multocida* bacterin-toxoid (BT) conferred protective immunity in rabbits against PMT challenge (553). To prevent vertical transmission of *P. multocida* from sows to suckling pigs or laterally among young weaned animals, sows are often vaccinated once or twice prior to farrowing to induce passive immunity through colostrum (542, 554–557). However, despite the benefits of PMT-based vaccination for prevention of atrophic rhinitis and other disease symptoms in swine and rabbits (543, 544, 553, 555, 557–559), current commercial and experimental vaccines do not confer complete immunity to *P. multocida* infection and are not effective in clearing the bacteria (542, 551, 555). Although PMT activates dendritic cells, it is a poor adjuvant and appears to suppress the antibody response *in vivo* (497). PMT is nonetheless an effective immunogen, and mutant derivatives have shown potential for vaccine development against atrophic rhinitis (543, 544, 549–551, 555, 557, 560, 561).

Several of the *Pasteurella* outer membrane proteins are putative virulence factors and potential targets for vaccine development (reviewed in reference 433). For example, antisera against the outer membrane protein Oma87 protected mice against a lethal-dose challenge of *P. multocida* (447). Vaccination with recombinant adhesion protein Cp39 from *P. multocida* strain P-1059 protected chickens from challenge with strain P-1059 (serotype A:3) and strain X-73 (serotype A:1) (436, 448). OmpH-specific antibodies were more effective than OmpA-specific antibodies in curbing *P. multocida* growth in mice, presumably by enhancing PMN phagocytosis (562). Full-length OmpH was more effective than shorter fragments as a vaccine against a swine strain of *P. multocida* (isolated from a case of atrophic rhinitis) in a mouse challenge model (563). Although OmpA elicits a strong antibody response, vaccination is not protective in a mouse model of infection (435). The type 4 fimbrial subunit of serotype A, B, and D strains has been identified as a potential vaccine candidate (439, 449); however, efficacy as a vaccine has been reported only for the fimbrial protein from serotype B:2 against hemorrhagic septicemia in goats (564).

Using a bioinformatics approach, 98 genes in avian strain Pm70 and 107 genes in the nontoxinogenic porcine strain 3480 were identified as encoding putative OMPs (415). Of this combined list, 71 recombinant proteins were expressed and purified, albeit most as insoluble proteins, and tested as vaccine candidates. Only one protein, lipoprotein E (PlpE), was found to protect against *P. multocida* challenge in chickens and mice, which confirmed previously reported results using the PlpE cloned from the avian serotype A:1 strain X-73 (446). However, a *plpE* knockout mutant strain retained full virulence (416). Conjugated vaccines comprised of multiple antigens, such as OmpH plus PlpE peptides, have also shown promise (445, 565).

Additional vaccine candidates include the filamentous hemagglutinin protein (FhaB2) (566), iron-regulated Omps (567–570), and LPS (109). Vaccination with peptides derived from FhaB2 protected turkeys from fowl cholera upon challenge with *P. multocida* P1059 (566). LPS is a major virulence factor and immunogen of *P. multocida*, but its potential use and efficacy as a vaccine candidate is complicated by the structural heterogeneity of the 16 different serovars (109). Several *in vivo*-expressed surface antigens have been identified as potential vaccine candidates (72, 538, 571). A number of these are iron-regulated Omps expressed during *P. multocida* infection and have been characterized as potential immunogens in challenge studies (568–573). For example, the 96-kDa heme acquisition system receptor (HasR) protein is a surface-exposed Omp conserved among most *P. multocida* isolates. HasR is expressed under low-iron conditions *in vivo* and confers protection against challenge with bovine *P. multocida* serotype A:3 strain 232 (568). A whole-cell vaccine based on a serotype A:1 strain of *P. multocida* that has been inactivated by treatment with high iron concentrations has also been explored (574).

A few bacterin- and/or toxin-based vaccines are available commercially. For example, Porcillis AR-T DF is a PMT-based vaccine comprised of a deletion mutant of PMT (Δ28-148) plus inactivated *Bordetella bronchiseptica* bacterin. A commercial vaccine against fowl cholera (chickens and turkeys), sold as CholeramuneM, Multimunem, or M-Ninevax-C, is available and is based on a freeze-dried preparation of a live, avirulent avian isolate of *P. multocida* M-9 strain (a serotype A:3-A:4 cross). A trivalent combination vaccine against fowl cholera (for ducks, chickens, and other poultry) and rabbit pasteurellosis, sold as Landavax, is available as an inactivated bacterin oil emulsion of *P. multocida* serotype A:1, A:3, and A:4 strains. A tetravalent combination vaccine, sold as Rhini ShieldTX4, provides four-way protection against

swine PMT-mediated atrophic rhinitis and respiratory diseases through a bacterin containing inactivated *B. bronchiseptica*, *Erysipelothrix rhusiopathiae* (the causative agent of erysipelas), *P. multocida* serotype A, and toxinogenic *P. multocida* serotype D. A tetravalent *Pasteurella* OBP vaccine for cattle that is a formalinized bacterin of *P. multocida* serotypes A, D, and E plus *M. haemolytica* serotype A:1 is also commercially available.

FUTURE PERSPECTIVES

Extensive genetic, biochemical, and virulence studies of *P. multocida* and other *Pasteurellaceae* have provided valuable insights into the disease processes of these organisms in their natural hosts and have led to the development of new non-bacterin-based vaccines, several of which are now available commercially for animal use. With the impressive advances that have been made, we are at a cusp in regard to our understanding of the molecular virulence mechanisms of *P. multocida* pathogenesis. Pathogenomics and ribotyping, in particular, have greatly contributed to our ability to distinguish among the various clinical isolates for diagnostic purposes and epidemiological studies and have provided glimpses of the relatedness among the *Pasteurellaceae*.

In addition to furthering our understanding of the role of capsule and LPS biosynthesis, antibiotic resistance, and PMT production in pasteurellosis, genome comparison has begun to identify additional virulence genes responsible for host specificity and other phenotypes. Major advances are on the horizon with the information gleaned from comparison of existing and additional genomes of *P. multocida* and other related *Pasteurellaceae* in the pipeline, as well as from *in vivo* transcriptional and protein expression profiling studies such as RNA-seq and proteomics technologies. Greater understanding of the molecular and immunologic mechanisms of pathogenesis will provide insights into the host-microbe interactions involved in chronic infection and the molecular basis of the transition from subclinical or chronic disease to acute, disseminated disease. These studies will also provide clues about the long-term sequelae of exposure to chronic or acute infections with these organisms.

Our interactions with pets and other domestic and wild animals are unlikely to diminish in the future. Mounting evidence suggests that such contacts that result in *P. multocida* infection can lead to outcomes ranging from benign to disastrous. Considering the high prevalence of *Pasteurella* species as part of the microbiota of domestic and wild animals, it would be prudent for us to consider zoonotic transmission of *P. multocida* as a serious risk for infection.

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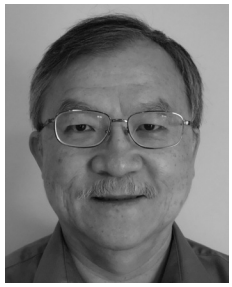

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