Scientific article

Efficient identification and characterization of pathogenic bacteria in veterinary diagnostics. Part II.

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Abstract: We present a method for the efficient and reliable identification of pathogenic bacteria of significance in veterinary and human medicine. The QIAxcel® Advanced was used to separate and analyze PCR products to successfully identify *Brachyspira hyodysenteriae*, *Brucella* sp., ESBL-producing bacteria, *Listeria monocytogenes*, *Renibacterium salmoninarum*, and *Taylorella equigenitalis*. The associated QIAxcel ScreenGel® software enabled automated analysis and identification of the pathogens, thereby minimizing manual intervention and yielding reproducible and accurate results.

Introduction

Rapid and accurate identification of pathogens in veterinary medicine is the cornerstone for a successful battle against animal infectious diseases that can seriously endanger also human populations. The widespread use of antibiotics has led to the development of an increasing number of antibiotic-resistant bacteria, which may cause significant health problems in both humans and animals, the latter of which are considered an important source of resistant strains. Consequently, it is of great clinical and commercial interest to define methods that enable rapid and efficient identification of pathogens to support appropriate measures for the benefit of animal and public health.

Materials and methods

For the purpose of this evaluation, we used isolates of *Brucella* sp., extended-spectrum beta-lactamases (ESBL)-producing bacteria, *Listeria monocytogenes* and *Taylorella equigenitalis* that were collected in the scope of routine and research work performed at our institute. DNA was extracted from cultures using a simple lysis: colonies were suspended in PCR-grade water, boiled at 100°C for 15 min and centrifuged at 12,000 rpm for 2 min. The supernatant was used for PCR without further purification. DNA for detection of *Renibacterium salmoninarum* was extracted from fish kidneys using a commercial DNA extraction kit for tissue samples. DNA for detection of *Brachyspira hyodysenteriae* was extracted from intestinal contents/feces using a commercial DNA extraction kit adapted for fecal samples.

For each pathogen, references related to individual PCR assays are cited in the respective sections. The subsequent electrophoretic analysis of PCR products was identical for all tested samples. Using the QIAxcel capillary electrophoresis system, the amplicons were separated with the QX DNA Screening Kit employing ▶

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the AM420 method with the following electrophoresis parameters: alignment marker injection at 4 kV for 20 s, sample injection at 5 kV for 10 s, and separation at 5 kV for 420 s. The alignment markers 15 bp–1 kb or 15 bp–3 kb and the DNA size markers 50–800 bp and 50 bp–1.5 kb were run simultaneously.

The selected genes listed in Table 1 were targeted in pathogen-specific PCR assays and subsequently identified by the QIAxcel ScreenGel software. The established PCR protocols followed by an optimized analysis procedure on the QIAxcel Advanced yielded clear results, as seen in Figures 1–6.

Table 1. Overview of genes targeted in specific PCR assays

Bacterium	Gene*	Amplicon size (bp)*
Brachyspira hyodysenteriae	*nox*	354
Brucella abortus biovar 1, 2, 4	IS*711*	498
B. melitensis biovar 1, 2, 3		731
B. ovis		976
B. suis biovar 1		285
ESBL-producing bacteria	bla_{TEM}	963
	$bla_{CTX\text{-}M\text{-}1\ group}$	754
	$bla_{CTX\text{-}M\text{-}9\ group}$	857
Listeria monocytogenes	*prfA*	274
	prs	370
	lmo0737	691
	lmo1118	906
	orf2819	471
	orf2110	597
Renibacterium salmoninarum	*p57*	501
Taylorella equigenitalis	16S rDNA	585

* References are provided in the respective text sections.

Results and discussion

Brachyspira hyodysenteriae

Two pathogenic species of anaerobic intestinal spirochetes colonize pigs, *B. hyodysenteriae* and *B. pilosicoli*.

B. hyodysenteriae causes swine dysentery, characterized by severe diarrhea with blood, mucus and white fibrin-debris grains. Recovered pigs can become asymptomatic carriers and act as a source of the bacteria (1). Enteric diseases in pigs can result in devastating economic losses due to reduced production and the high cost of treatment and preventative measures. Because of this economic impact, laboratories should implement rapid diagnostic methods (2). The brachyspiras are fastidious, oxygen-tolerant anaerobes that are difficult to culture and identify correctly. Molecular methods overcome these diagnostic problems.

In our laboratory, we use a conventional PCR described by La et al. (3) for the detection of *B. hyodysenteriae* in fecal or intestinal samples and for determination of *Brachyspira* isolates. The PCR targets a 354 bp region of the NADH oxidase (*nox*) gene that is specific for *B. hyodysenteriae* (Figure 1).

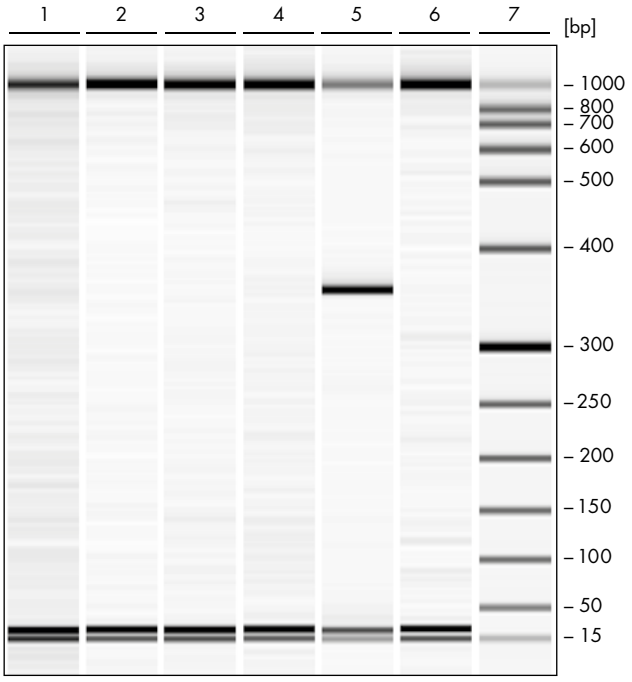

Figure 1. PCR product analysis of *B. hyodysenteriae* on QIAxcel. A 354 bp region of *nox* was amplified. **Lanes 1–4** contain negative samples, **lane 5** a positive control, and **lane 6** a negative control. **Lane 7** displays the DNA size marker 50–800 bp.

Brucella sp.

Brucellosis is a major bacterial zoonosis of global importance. The causative agents are members of the genus *Brucella* and affect a wide range of mammals, including humans, cattle, small ruminants, pigs, rodents, wildlife and marine mammals. In animal hosts, the disease affects the reproductive system primarily with concomitant loss in productivity of affected animals (4). Worldwide, the main pathogenic species in domestic animals are *B. abortus*, responsible for bovine brucellosis, *B. melitensis*, the main cause of small ruminant brucellosis, and *B. suis*, responsible for swine brucellosis. *B. ovis* and *B. canis* cause ram epididymitis and canine brucellosis, respectively. Some species have been subtyped into biovars based on phenotypic traits.

Brucellosis is not a sustainable disease in humans. The source of human infection always resides in domestic or wild animal reservoirs. *B. melitensis* is the most important zoonotic agent, followed by *B. abortus* and *B. suis* (5). Human brucellosis is characterized as an acute febrile illness which may progress to a more chronic form and can produce serious complications affecting the musculoskeletal, cardiovascular and central nervous systems. There is an occupational risk to veterinarians and farmers who handle infected animals, aborted fetuses or placentas. Brucellosis is one of the most easily acquired laboratory infections (6).

Due to the complexity and length of classical phenotypic identification methods for brucellas, numerous PCR assays have been developed, including assays to differentiate among *Brucella* species and/or biovars. These assays target genetic loci that are variable among the species/biovars. Such targets are uncommon in *Brucella* since the genus is remarkably homogeneous. While some large deletions or rearrangements have been reported within a species or biovar, most genetic differences consist of single nucleotide polymorphisms (SNP). The first PCR-based assays focused on genus-specific loci for identification. More specific PCR assays were developed later. Bricker and Halling (7) designed the multiplex AMOS PCR assay, which can identify and differentiate *B. abortus* biovars 1, 2 and 4, *B. melitensis*, *B. ovis* and *B. suis* biovar 1. The assay was subsequently modified to include strain-specific primers for the two commonly used vaccine strains, S19 and RB51 (8).

We used AMOS PCR for years in our laboratory but eventually replaced it with the commercially available INgene Bruce-ladder V PCR kit (Ingenasa, 9) which enables detection and differentiation of *B. abortus*, *B. melitensis*, *B. ovis*, *B. suis* (Table 2) and the vaccine strains RB51, B19 and Rev1 (Figure 2).

Table 2. Interpretation of *Brucella* sp. identification results from the INgene Bruce-ladder V PCR Kit (Ingenasa)

Species	PCR product size (bp)
Brucella suis	1682/1071/587/272
B. abortus	1682/587
B. melitensis	1682/1071/587
B. ovis	1071/587
Vaccine strain RB51	2524/587
Vaccine strain B19	1682
Vaccine strain Rev1	1682/1071/587/218

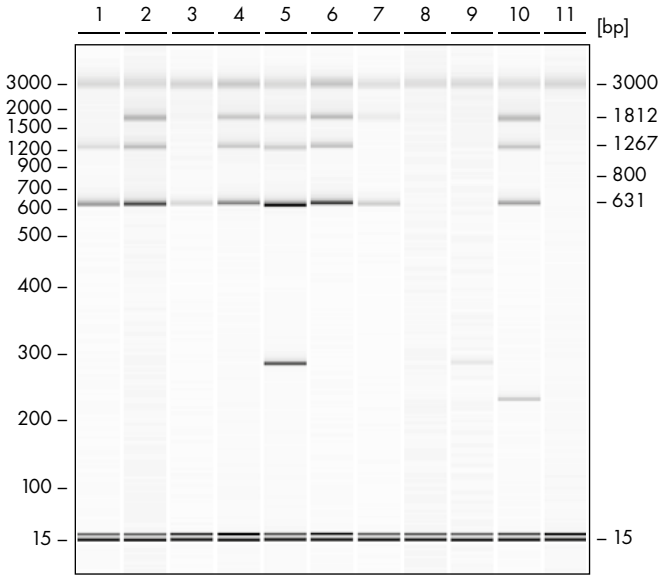

Figure 2. PCR product analysis of *Brucella* sp. on QIAxcel. The IS*711* gene was amplified using the INgene Bruce-ladder V Kit. The brucellas identified are *B. ovis* in **lane 1**, *B. melitensis* in **lanes 2, 4** and **6**, *B. suis* in **lane 5**, and *B. abortus* in **lane 7**. The samples in **lanes 3** and **9** could not be identified and **lane 8** contains a negative sample. **Lane 10** contains a positive control and **lane 11** a negative control.

Extended-spectrum beta-lactamases (ESBL)-producing bacteria

These bacteria are commonly *Enterobacteriaceae* and non-fermenting bacteria. *Escherichia coli*, *Salmonella* sp. and *Klebsiella* sp. are the most important ESBL producers (10). These bacteria express extended-spectrum beta-lactamases that hydrolyze extended-spectrum cephalosporins with an oxyimino side chain, such as cefotaxime, ceftriaxone, ceftazidime, and the oxyimino-monobactam aztreonam. Genes encoding ESBL are usually located on transferable plasmids which also carry resistance genes for other types of antimicrobials (i.e., fluoroquinolones, aminoglycosides). Initially, ESBLs were only found in humans, but have since been identified in animals (companion animals, livestock, food-producing animals) with increased frequency. This observation leads to the hypothesis that animals and food could spread ESBL-producing bacteria and such reservoirs can be potential sources of resistance genes for human pathogens (11). Three families of ESBL enzymes are frequently found in food and animals, TEM, SHV and CTX-M groups (12). Shown are the results from 3 PCR assays targeting bla_{TEM}, $bla_{CTX\text{-}M\text{-}1\ group}$ and $bla_{CTX\text{-}M\text{-}9\ group}$ (protocols from the EU Reference Laboratory for Antimicrobial Resistance; EURL-AR). These PCR assays are a useful tool for the detection of the most common ESBL genes in bacteria isolated from food (e.g., poultry meat) and animal feces (Figures 3–5). ▶

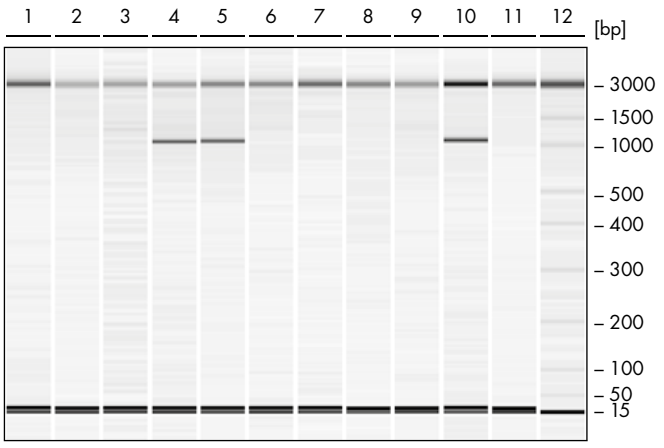

Figure 3. PCR product analysis of TEM beta-lactamases in *E. coli* isolates on QIAxcel. Lanes 1–3 and **6–9** contain negative samples, **lanes 4** and **5** positive samples, **lane 10** a positive control, and **lane 11** a negative control. **Lane 12** displays the DNA size marker 50 bp–1.5 kb.

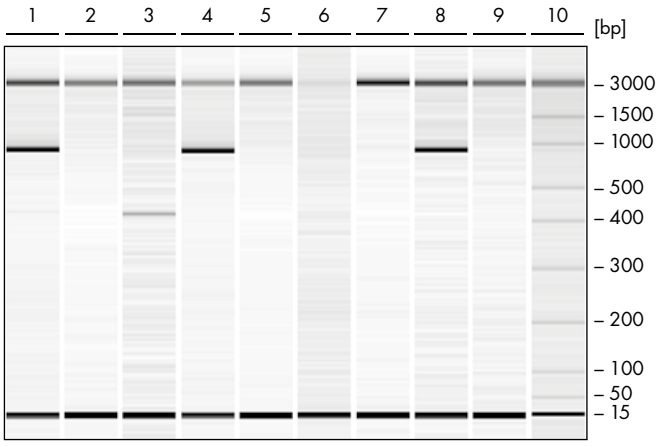

Figure 4. PCR product analysis of CTX-M-1 group beta-lactamases in *E. coli* isolates on QIAxcel. Lanes 1 and **4** contain positive samples, **lanes 2**, **3**, **5-7** negative samples, **lane 8** a positive control, and **lane 9** a negative control. **Lane 10** displays the DNA size marker 50 bp–1.5 kb.

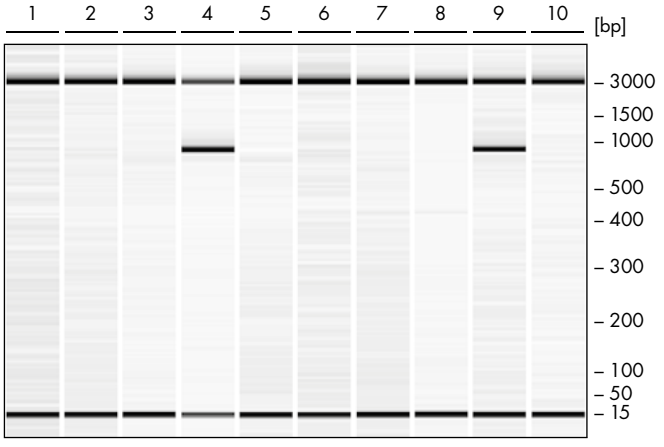

Figure 5. PCR product analysis of CTX-M-9 group beta-lactamases in *E. coli* isolates on QIAxcel. Lanes 1–3 and **5–8** contain negative samples, **lane 4** a positive sample, **lane 9** a positive control and **lane 10** a negative control.

Listeria monocytogenes

Bacteria of the genus *Listeria* cause listeriosis, which afflicts both animals and humans (13). The causative agent is most often *L. monocytogenes*. In infected herds, a substantial proportion of animals is asymptomatic and carriers may shed *L. monocytogenes* in feces and milk (14). Transmission to humans most commonly occurs by consumption of raw animal products (15), especially foods contaminated during manufacturing and post-processing (16, 17). In humans, foodborne listeriosis usually occurs in pregnant women, neonates or immunocompromised adults (18). *L. monocytogenes* is the most important cause of death from foodborne infections in industrialized countries and although human infections are rare, they are important given the associated high mortality rate (14).

Molecular detection of *L. monocytogenes* in clinical or food samples is usually performed after cultivation on agar plates or culture enrichment in liquid medium. *L. monocytogenes* serotyping of, for example, food and human isolates is required as a first level of discrimination and is based on differences in somatic flagellar antigens. Routine typing is performed by conventional serum agglutination, but the various disadvantages of this method make the more useful and rapid molecular serotyping a welcome alternative. Two PCR assays have been developed to classify *L. monocytogenes* into 5 of the most common molecular serological groups, a multiplex PCR targeting 6 genes (19) and a PCR targeting a single gene (20). The latter is performed because of the occurrence of some atypical *L. monocytogenes* strains. In our laboratory, both assays were implemented according to the instructions given by the EU RL for *L. monocytogenes* (21). The multiplex PCR assay targets *orf2819*, *orf2110*, *lmo0737*, and *lmo1118* to assign serotypes (19), *prs* to confirm the genus (19), and *prfA* to confirm the species (22, a modification of the reverse primer in 21) (Figure 6A). The PCR assay exhibits equal or better performance compared to classical serotyping, and is therefore promoted as the method of choice. Due to the large number of samples processed on a regular or periodical basis, molecular typing is more convenient. Since electropherogram superposition is possible with QIAxcel (Figure 6B), the comparison of results from samples to positive controls is less laborious and more reliable when reporting which of the multiplex targets are present in individual samples. The benefit is particularly apparent when some of the amplification products in the

multiplex reaction are less intense, as is often observed in *L. monocytogenes* serotyping (Figure 6A).

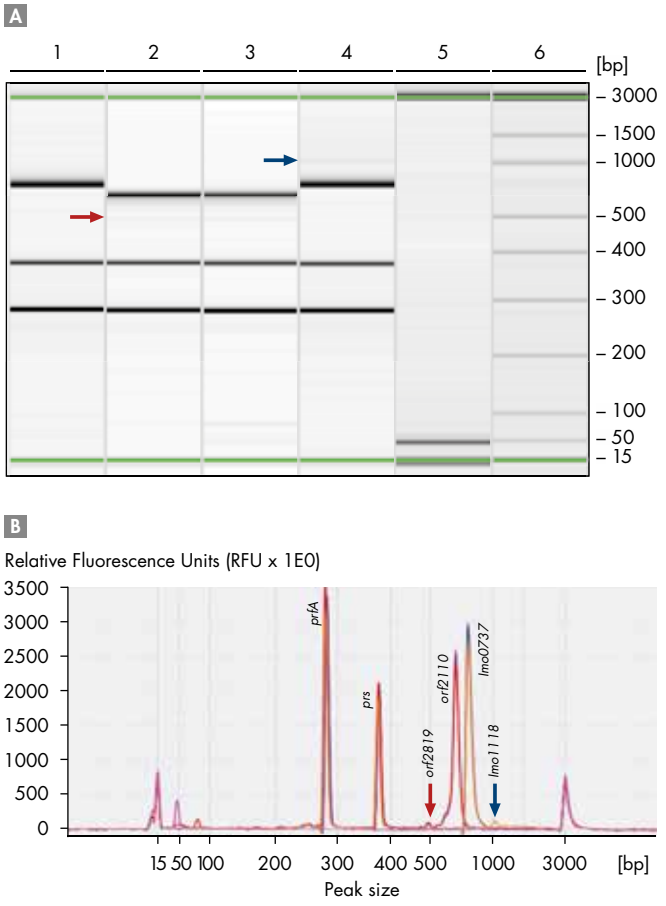

Figure 6. PCR product analysis of *L. monocytogenes* strains on QIAxcel. A Visible in **lane 1** of the gel image is sample 1 with identified genes *prfA*, *prs* and *lmo0737*. In **lane 2**, *prfA*, *prs*, *orf2110* and *orf2819* were identified in sample 2, although the last gene was poorly discernible (red arrow). **Lane 3** contains a positive control with the same genes as in lane 2. Genes *prfA*, *prs*, *lmo0737* and *lmo1118* of a positive control were identified in **lane 4** but the last is poorly discernible (blue arrow). **Lane 5** contains a negative control and **lane 6** displays the DNA size marker 50 bp–1.5 kb. B An electropherogram of results in superposition mode clearly shows the genes *prfA*, *prs*, *orf2110* and *orf2819* in **lane 2**, although the latter gene was poorly discernible in the gel image (a positive control, red line). Amplicons *prfA*, *prs*, *lmo0737* and poorly discernible *lmo1118* are visible in **lane 4** (positive control 2; orange line). **Lane 5** contains a negative control (pink line). Samples from lanes 1 and 2 are shown (blue line superpositioned on control lines), clearly indicating the presence of *prfA*, *prs* and *lmo0737* in sample 1 and *prfA*, *prs*, *orf2819* and *orf2110* in sample 2.

Renibacterium salmoninarum

Bacterial kidney disease (BKD), a slowly progressing systemic infection caused by *R. salmoninarum*, occurs in most parts of the world where wild or cultured salmonids are found (23). As one of the most important bacterial diseases affecting cultured salmonids, BKD causes high morbidity and mortality in susceptible species. Outbreaks of BKD are most frequently recorded among farmed fish but cases of clinical BKD have also been detected in wild fish, including naturally spawning populations that have never been supplemented with hatchery fish. *R. salmoninarum* is transmitted both horizontally from infected fish sharing the water supply and vertically through eggs from infected parents, which aids to the persistence of the pathogen in fish populations. *R. salmoninarum* is often enzootic in wild salmonid populations and hatchery fish are constantly exposed to bacteria shed into the water by wild fish residing upstream. As with other infectious diseases of salmonids that are difficult or impossible to treat, avoidance is recommended for the control of BKD in cultured salmonid stocks (24).

A PCR assay first described by Brown et al. (25) using primers targeting the gene that encodes the p57 protein was implemented to detect *R. salmoninarum* in fish tissue. (Figure 7).

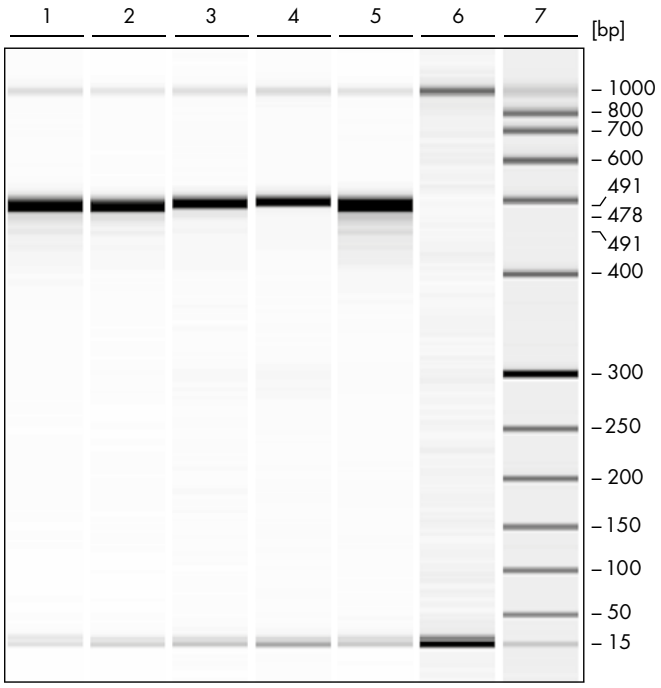

Figure 7. PCR product analysis of *R. salmoninarum* on QIAxcel. The gene that encodes the p57 protein was amplified. **Lanes 1–4** contain positive samples, **lane 5** a positive control, and **lane 6** a negative control. **Lane 7** displays the DNA size marker 50–800 bp.

As we receive only a few samples per year to be investigated for BKD, maintaining the culture method for *R. salmoninarum*, which requires special growth media, is hard to justify. In addition, the PCR assay is considerably faster compared to cultivation, which may take weeks due to the slow growth of the bacterium on artificial media. The described PCR test is ▶

sensitive enough to detect as few as 2 bacterial cells per fish egg. The limit of detection for PCR performed with DNA extracted from kidney tissue is not described, but results with kidney samples are comparable to results with egg samples (25).

Taylorella equigenitalis

T. equigenitalis causes contagious equine metritis (CEM) in horses, a highly transmissible inflammatory disease of the proximal and distal reproductive tract of mares (26). Infection results in temporary infertility and is mostly transmitted by natural mating involving contaminated stallions or infected mares. The disease can spread rapidly from a single asymptomatic carrier, particularly a stallion mating with numerous mares, and greatly impacts international trade as reproductive success may be severely suppressed (27). The carrier status, which is possible in both stallions and mares, may persist for many months or years (28). Therefore, pre-breeding testing in endemic areas and surveillance screening before importation into CEM-free countries are obligatory and represent an additional economic burden.

Identification of the agent in clinical samples using conventional microbiological methods requires a highly experienced laboratory. *T. equigenitalis* is fastidious and difficult to grow; commonly taking 3–6 (and up to 14) days to display colonies (27). Molecular assays, PCR and real-time PCR, exist for direct (from swabs taken at sampling sites) or indirect (from cultures grown from swabs) detection of *T. equigenitalis*, enabling highly specific and sensitive identification (27). The process is also significantly faster in the case of direct detection (27).

Our laboratory uses a conventional PCR assay described by Bleumink-Pluym et al. (29). Identification of isolates is based on 16S ribosomal DNA sequences. Samples containing *T. equigenitalis* generate amplicons of 585 bp (Figure 8). The assay can also be used for direct detection in clinical samples as its sensitivity is higher compared to culture (29). Furthermore, results are not biased by the presence of background bacteria that may overgrow the slowly growing *T. equigenitalis* on culture plates, even with selective media (29). Culturing is more appropriate for carriers with high loads of *T. equigenitalis* but PCR is the method of choice for pre-breeding and surveillance screenings where many of the trace carrier animals are easily overlooked.

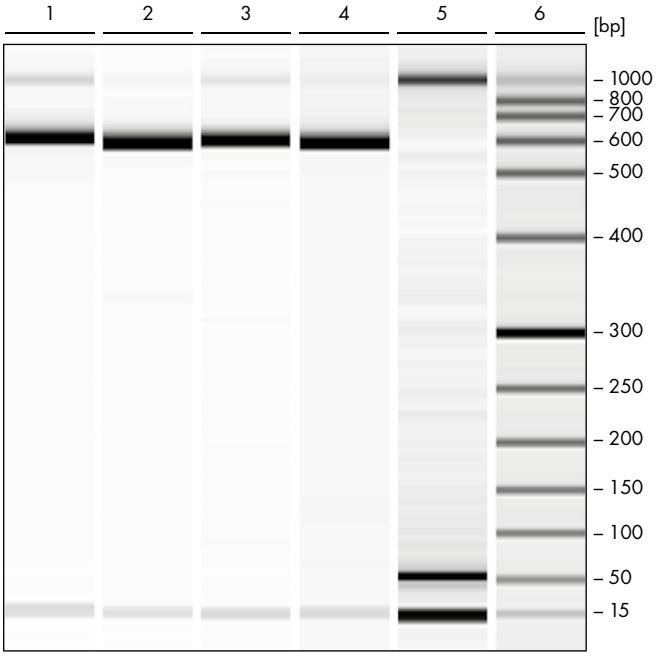

Figure 8. PCR product analysis of *T. equigenitalis* strains on QIAxcel. Amplicons of 16S ribosomal DNA are identified in **lanes 1–4**. **Lane 5** contains a negative control and **lane 6** displays the DNA size marker 50–800 bp.

Conclusions

With a growing need for fast and accurate identification of pathogenic bacteria, the QIAxcel Advanced for analysis of PCR products can make an important contribution to improving veterinary diagnostics.

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Ordering Information

Product	Contents	Cat. no.
QIAxcel Advanced Instrument	Capillary electrophoresis device: includes computer, QIAxcel ScreenGel software, and 1-year warranty on parts and labor	9001941
QIAxcel DNA High Resolution Kit (1200)	QIAxcel DNA High Resolution Gel Cartridge, Buffers, Mineral Oil, QX Intensity Calibration Marker, 12-Tube Strips	929002
QIAxcel DNA Screening Kit (2400)	QIAxcel DNA Screening Gel Cartridge, Buffers, Mineral Oil, QX Intensity Calibration Marker, 12-Tube Strips	929004
QX Alignment Marker 15 bp–3 kb (1.5 ml)	Alignment marker with 15 bp and 3 kb fragments	929522
QX Alignment Marker 15 bp–1 kb (1.5 ml)	Alignment marker with 15 bp and 1 kb fragments	929521
QX DNA Size Marker 50 bp–800 bp (50 ml)	DNA size marker with fragments of 50, 100, 150, 200, 250, 300, 400, 500, 600, 700, and 800 bp; concentration 100 ng/µl	929561
QX DNA Size Marker 100 bp–2.5 kb (50 µl)	DNA size marker with fragments of 100, 200, 300, 400, 500, 600, 700, 800, 1000, 1200, 1500, 2000, and 2500 bp; concentration 100 ng/µl	959559

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