Bovine Viral Diarrhea Virus Testing Options

Barrett D Slenning, *MS, DVM, MPVM*
Population Medicine Program, Department of Farm Animal Health and Resource Management
College of Veterinary Medicine, NC State University, Raleigh, NC 27606
ph: 919.513.6324, fax: 919.513.6464, email: barrett_slenning@ncsu.edu

Abstract

A review of bovine viral diarrhea virus (BVDV) dynamics is followed by a review of test efficiency measures. BVDV diagnostic challenges are then discussed with attention to its pathogenesis during pregnancy and fetal effects. Economic decision theory methods are then applied to evaluate BVDV testing efficiencies and outcomes given certain herd BVDV characteristics..

Two scenarios evaluated are ELISA antibody testing 1) an infected, naive herd, and 2) an infected, 70% immune herd. In the naive herd, 25% of cows were infected in the high risk 60- 120 day of gestation period. This resulted in a 78% calf crop, an 8% persistently infected (PI) prevalence, and where 5% of normal calves had titers. In the 70% immune herd, approximately 8% of cows were infected in the high risk period, resulting in a 90% calf crop, a 2% PI prevalence, and where 1% of normal calves had titers.

The scenarios yielded different test performances. For the naive herd, we were ~56% confident in positive test results, but ~100% confident in negative test results. In the partially immune scenario, these confidences were ~28% and ~100%, respectively. In the naive herd, we falsely culled 3.9 calves, and missed 0.4 PI calves. In the other scenario, the numbers were 3.5 calves, and 0.1 PI calves, or a 10% reduction in false culls, and a 75% reduction in missed PI animals, in spite of the worse test results. This suggests that, though it impairs test performance, the higher a herd's immunity, we can quantify improved outcomes.

Introduction

Bovine viral diarrhea virus (BVDV), a member of the *Pestivirus* genus, has long been recognized to be the causative agent for ill-health and large economic losses in both beef and dairy cattle. Since the 1980's, because of the nearly simultaneous arrival of molecular techniques, and the Type II antigenic group of BVD, veterinary research has begun to plumb the pathogenesis and epidemiology of this pathogen. But we still do not clearly understand the entirety of BVDV's complex etiology, ecology, or population dynamics. BVDV produces variable manifestations in affected animals, in part due to the host's immunological competency, to the target's age or stage of gestation at exposure, and to the genotype, biotype and strain(s) of BVDV to which the host is exposed. There are also conflicting research reports on the efficacy of the various vaccines for protecting animals from BVDV infection, clinical manifestations and between-animal transmission. As a result of this multifactorial etiological web, we deal with any single herd likely having several different 'risk groups' with regard to BVDV status: 1) naive animals; 2) vaccinated animals; 3) pregnant animals and their fetuses; 4) acutely infecteds, and 5) persistently infected animals.

Other authors and speakers in this session will explore the virulence factors, etiologic nuances and immunological complexities involved in producing such a panoply of effects — this paper will, therefore, not address current research in BVDV biology, except where it bears upon BVDV diagnostic problems (and some potential solutions) facing veterinarians. This means, however, that I will make assumptions about the readers' level of understanding of BVDV dynamics – but don't worry, those areas will be covered (to a much better degree than I could hope to do!) by the others in this session. This presentation, then, will comprise four related modules: 1) background information on how we determine clinical test efficiency; 2) how the above Risk Groups' characteristics complicate clinical testing; 3) the different types of BVDV tests currently available; and 4) a decision process to help us make some valid (hopefully) recommendations to our clients regarding BVDV.

Basics of Clinical Test Efficiency Measures

Sensitivity and specificity – the 'Pillars' of test efficiency indices

Most of us have seen *ad nauseam* depictions of different clinical tests' SE and SP. Nearly every time someone even mentions SE or SP, they immediately throw a 2*2 table up, thinking the table is self explanatory. Often we vaguely understand what the presentations mean, but just as often we feel they are a little removed from the reality of interpreting tests. Those impressions are fundamentally correct: SE and SP are, in and of themselves, of limited usefulness to someone in the field trying to figure out what's what with a herd, and

the standard 2*2 table, while helpful, assumes we have perfect knowledge of test quality and animal classification. Of course, if we had perfect information, we wouldn't be running clinical tests! But we muddle on, nonetheless.

First some definitions: The **Sensitivity (SE)** of a test is a measure of that test's ability to identify true positives, given the tested group is truly positive. In a standard 2*2 table presentation (yes, I am going to resort to one of these things! See to Figure 1), it is given by the cell signifying the positive agreements (CELL A) between the test and a gold standard divided by the marginal total of truly diseased animals (CELL A+C). The higher a test's SE, the better the test at pulling truly diseased animals from a group. The **Specificity (SP)** of a test is a measure of that test's ability to distinguish true negatives, given the tested group is truly negative (in the 2*2 table : CELL D / CELL B+D); the cell signifying the negative agreements divided by the marginal total of truly negative animals. The higher a test's specificity, the better the test is at identifying non-diseased animals and leaving them be. For the IHC and PCR comparison, the PCR displays a SE of 97.3% and a SP of 90.5% – meaning the PCR will detect 97.3% of those animals testing positive to IHC, and will correctly identify 90.5% of those animals testing negative to IHC.

Well, that seems clear enough. So why do we often feel uncomfortable with SE and SP? Because each is calculated using only one side of the 2*2 table (i.e., either the gold standard positive or the gold standard negative side), meaning that neither is affected by prevalence of disease. The information we want (i.e., the likelihood that an animal a test labels "positive" is truly diseased) needs to be calculated using both sides of the table (i.e., either the total number of test positives or the total number of test negatives). The "horizontal" alignment of the values of interest, thusly, means that they are affected by prevalence — for example, the ratio of true positives to false positives (a:b, in above table) effects our confidence that a test positive animal is truly diseased (with the ratio of c:d similarly effects our confidence in test negative results). In other words, while SE does tell us how good a test is in identifying diseased animals, the false positive rate (1-SP), unfortunately, also throws in incorrectly classified animals into the mix. It makes sense, then, that when the prevalence of a disease is very high, the impact of the false positive rate will be diminished. Conversely, in situations of very low disease prevalence the false positive rate might comprise the majority of animals testing positive. The same, but inverse, dynamic occurs with SP and the false negative rate (1-SE).

What we, as practitioners, are interested in are what are called the 'predictive values' of our tests. The predictive values for either positive tests, or negative tests, are calculated as **a / (a+b)** and **d / (c+d)**, respectively. Using the tables in Figure 1, for the PCR vs IHC comparison, the PCR test displays a '**Predictive Value, Positive**' (PVP) of 36/90 = 40.0%, and a '**Predictive Value, Negative**' of 517/518 = 99.8%. The predictive values tell us that, in a relatively low prevalence situation, the likelihood a PCR test positive animal actually has BVD is 40%, and that a PCR test negative animal actually does not have BVD is just about 100% – all relative to IHC. In other words, our animals that tested positive are actually 1.5 times more likely to not have the disease than they are to be diseased, but we can be close to certain that cows testing negative truly do not have the disease.

Though the numbers will change with different tests, this relationship of tests increasing in inefficiency at either extreme of disease prevalence holds true. Take, for example, data from a test manufacturer (IDEXX Corp., from their website. 2003) for an ELISA anti-BVDV antibody test (see Figure 2). In this figure we also introduce the concept of approximate **confidence intervals** (CI) for the efficiency indices.[8] Our confidence in the precision of any percentage estimate is, in part,

Generic Two-By-Two Table for Depicting/Deriving Test Sensitivity, Test Specificity and Disease Prevalence

		Gold Standard Tes			
		Disease +	Disease -		
Test +		a	b	a+b	Sensitivity (SE) = a / (a+c)
Test -		c	d	c+d	Specificity (SP) = d / (b+d)
		a+c	b+d	total	Prevalence (PREV) (a+c)/total

Reverse-Transcription Polymerase Chain Reaction (PCR) versus Immunohistochemical Staining, in Tissues (IH ***[IHC used as "gold standard"]***

		IHC			
		Disease +	Disease -		
Test +		36	54	90	Sensitivity (SE) = 97.3%
Test -		1	517	518	Specificity (SP) = 90.5%
		37	571	608	Prevalence (PREV) 6.1%

Figure 1. Depiction of typical 2*2 table used to generate SE and SP, along with example comparing PCR and IHC in diagnosing BVDV (Derived from Mahlum CE, Haugerud S, et al [2002]).

Comparing IDEXX BVD Antibody Test vs Serum Neutralizati

		Disease status (SN gold standard)				calc'd	95% Conf Int
		Disease +	Disease -		PREVAL	70%	51% - 90%
Test +		19	1	20	SENSITIV	98%	91% - 100%
Test -		0	7	7	SPECIFIC	88%	73% - 100%
		19	8	27	PV POS %	95%	85% - 100%
					PV NEG %	95%	84% - 100%
					FALSE+ %	5%	0% - 15%
					FALSE- %	5%	0% - 16%

Figure 2. Test evaluation and efficiency derivation for a commercial BVDV antibody test (derived from IDEXX, 2003).

due to sample size. The Fleiss approximate CIs give us some idea of how 'soft' our estimates really are. For instance, given that 27 animals were used in this demonstration, the SE estimate of 98% has a 95% CI of 91%-100%. This can be interpreted as indicating that a SE of anywhere from 91% through to 100% is compatible with these data. Likewise, the estimates for PVP and PVN each show a high degree of spread – from the mid-80% range on up. Note, however, that the prevalence (PREV) for this sample is pretty high at 70%.

What would happen to our PVP and PVN estimates at different PREVs? The easy thing to do is solve the 2*2 table at different prevalences, as was done for Figure 3. Note how the PVP drops, and PVN goes up, as prevalence decreases. The opposite occurs as prevalence rises. We can interpret this chart to suggest that in a 27 head herd with a BVDV prevalence of 20%, we could be around 65% confident that test positives were truly infected (95% CI approximately 45% - 85%). Had the original herd been comprised of 10 times the number of cows (i.e., herd size = 270), that 95% confidence interval would have condensed to an approximate range of 60% - 72% (calculations not shown). Neither the SE nor SP of the test changed; the test performance did. By normal standards, this ELISA test is good. But when the disease is relatively unlikely, we cannot claim a high confidence when we identify an animal as a test positive. In a similar vein, when the disease is highly likely (i.e., prevalence is high) we lose confidence in our test when it claims an animal is test negative. No matter what kind of clinical test you are using – serology, titers, rectal pregnancy checking, records review – they all are similarly impacted at the extremes of prevalence. So our overall confidence in any test result is driven by the combination of test efficiency, disease prevalence and sample size.

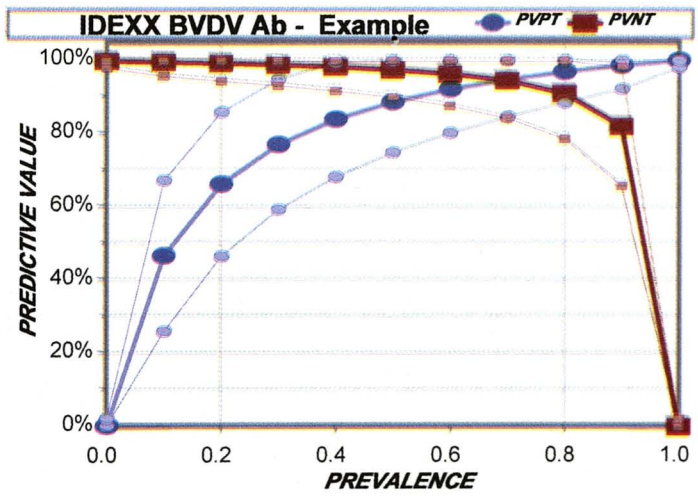


Figure 3. Change in predictive values with prevalence for the IDEXX antibody ELISA test from Figure 2. Small markers indicate 95% confidence intervals for the estimates.

Complications of Testing for BVD Due to Different Risk Groups Within a Herd

In the introduction we identified five basic risk groups within any individual herd: 1) naive animals; 2) vaccinated animals; 3) pregnant animals and their fetuses; 4) acutely infecteds, and 5) persistently Infected animals. As far as testing goes, the naive animals pose little trouble. Vaccinates can confuse our antibody-based tests, as they will show up as false positives if the test is run soon after vaccination. The last three groups, the pregnant animals, acutely infecteds (AI) and the persistently infected (PI) animals are the real pains when testing for BVD. Here we need to go into just a bit of BVD pathogenesis and host response to understand why.

Role of stage of gestation and BVD manifestation

Figure 4 is an illustration combining the described effects of BVDV infection based on stage of gestation at time of contact. This figure, however, assumes the pregnant animal is immunocompetent. If the pregnant animal is a PI, her calf will also be a PI. Hence, if a pregnant animal is infected with BVDV sometime after the first or second month, but before the fifth month of gestation, her calf will not respond to the virus, and (if the calf survives) will harbor the virus for life. These PIs are regularly cited as the major means of continuation and spread of BVD within cow-calf herds, dairy herds and stocker operations.[7] The impact of PIs on feedlot operations is generally regarded as unknown.[1] However, the fact that these animals can shed the virus for life and infect other animals means that identifying them is a priority in any herd control program. Being immuno-incompetent, PI animals' antibody tests will usually be negative, making these tests less than ideal for use in diagnosing BVDV in such animals. Such animals can, though, still mount a neutralizing antibody response, further confusing the situation.[4] PI animals tend to have high and long-lived BVDV viremias, a tendency that can be used in serial sampling for differentiation of PIs from acutely infected (AI) animals.[2] Additionally, a calf displaying both a negative antibody test, but a positive virus/antigen test, is very likely to be a PI.

A programmatic problem with identifying a PI calf after birth means that animal has some chance of transmitting BVDV to others before the test results/culling decisions occur, so identifying a pregnant animal while she is carrying a PI calf is desirable. Literature likelihood estimates that a dam carrying a PI calf is herself a PI are relatively low – a five state survey of 128 beef herds deduced that 7% of dams delivering PI calves were

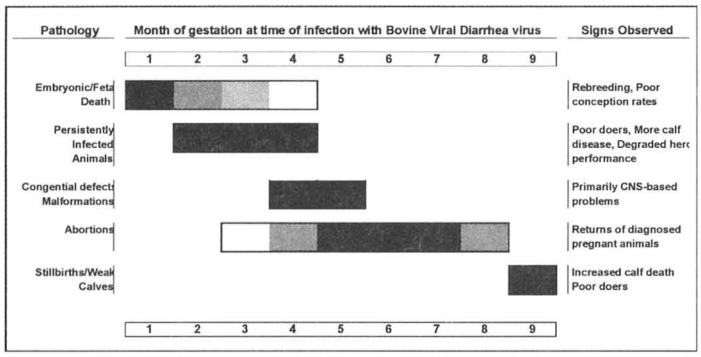


Figure 4. Approximate time-line correlating pathology and observed signs of BVD infection in an immuno-competent animal based on stage of gestation at time of infection. Darkness of cell is proportional to relative likelihood of occurrence. *Adapted from Brock (2003a); Cortese VS, et al (1998); Cree J (2003); Ishmael S (1999); Penn State Vet Sci Extension (2000).*

PIs themselves.[19] Hence, the majority of PI calves are born to dams who were acutely infected during gestation. One promising avenue for identifying cows carrying PI calves is currently in use in the Swedish BVD Control Program.[9] The technique depends on the relationship between anti-BVDV titer (in this study measured by Optical Density of an indirect ELISA) and stage of gestation in immunocompetent dams carrying PI calves. A PI fetus is viremic, and the dam is exposed to the virus, inducing an immune response in the dam. As a result of continued exposure, the titer of the dam shows a general, linear increase from mid-gestation on. In dams carrying non-PI fetuses, no such viremic exposure occurs, and the dam's titer remains relatively constant – assuming no acute exposures occur. The later in gestation, in general, the better the test's positive predictive value — in this study, the 95% CIs for titers in PI-carrying vs non-PI-carrying dams did not cross from 6 months gestation on. While this may be impractical for many commercial cow-calf operators, any producer handling his pregnant cows during the last trimester of pregnancy may consider this tactic.

Different BVD Tests Available

As with most viral tests, we have BVD tests that rest in two broad categories: those that identify anti-BVDV antibodies (Ab Tests), and those that identify the presences of virus. The latter group of tests can be further dichotomized into those that isolate and grow virus (VI), and those that demonstrate virus proteins/antigens (Ag tests). Unfortunately, the nomenclature across labs, companies, research groups and countries is not as clear as it could be, making it somewhat confusing at times to know just what is actually going on. Following is a short list of the most commonly available tests for BVD. Please note that this is in no way an all-inclusive list.

Antibody tests

These days, a practitioner asking for an anti-BVDV antibody test will be offered either the tried and true serum neutralization test (SN), or one of the enzyme linked immunosorbent assay (ELISA) -based tests. The SN test is often used as the 'gold standard' for comparisons. Both types of tests tend to show high sensitivities for exposed and reactive animals, but can be lacking in specificity depending on the vaccination status of the tested animals. PIs will not, by definition, be usefully identified using antibody-based tests. SN and ELISA tests tend to be fairly quick in turn-around. Be aware, however, that laboratory choice of analytical viral strain, cell culture line and technique can, at least for SN, make lab-to-lab comparisons of results problematic.[18]

Antigen tests – virus identification / growth

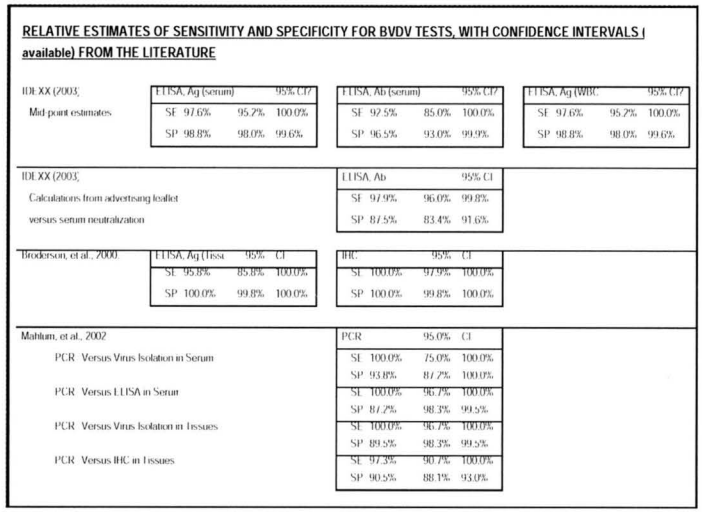
Virus isolation tests historically have depended on isolating and growing BVDV on cell culture. Such tests, across the board, tend to be 1) fairly low in sensitivity; 2) have a specificity of 100% (barring contamination); and 3) take a minimum of 2-4 weeks to complete. Remember that the virus may have come and gone before the clinical signs appear, making it likely that antigen tests will yield false negatives.

Antigen tests – virus antigen identification

This group of tests is perhaps the group with the most active ongoing body of research. The basic subgroupings of tests available here are 1) immunohistochemistry (IHC); 2) ELISA; and 3) polymerase-chain reaction (PCR) -based tests. The IHC, ELISA, and PCR subgroups have tests within them that can work off of either serum, leukocytes, or fixed tissues. IHC has, for long, been the other 'gold standard' against which to test other techniques. It can be relatively slow, but for all intents and purposes has no false positives if performed correctly. The newest subgrouping of these tests, PCR, has historically been limited in utility due to its exacting procedure requirements and cost. Recent advances in technology, however, have increased PCR's applicability to general clinical testing. Furthermore, the advent of immunohistochemistry capabilities utilizing 'ear-notch' specimens has greatly increased the ease and quality of specimen handling for virus identification.

Test performance

Figure 5 represents the findings of a non-exhaustive, non-scientific sampling of published test efficiencies for some of the more commonly available tests for



RELATIVE ESTIMATES OF SENSITIVITY AND SPECIFICITY FOR BVDV TESTS, WITH CONFIDENCE INTERVALS (

available) FROM THE LITERATURE

IDEXX (2003)

Mid-point estimates

ELISA: Ag (serum)		95% CI?
SE 97.6%	95.2%	100.0%
SP 98.8%	98.0%	99.6%

ELISA: Ab (serum)		95% CI?
SE 97.5%	85.0%	100.0%
SP 96.5%	93.0%	99.9%

ELISA: Ag (WBC		95% CI?
SE 97.6%	95.2%	100.0%
SP 98.8%	98.0%	99.6%

IDEXX (2003)

Calculations from advertising leaflet versus serum neutralization

ELISA: Ab		95% CI
SE 97.9%	96.0%	99.8%
SP 87.5%	83.4%	91.6%

Broderson, et al., 2000

ELISA: Ag (Tissu		95% CI
SE 95.8%	85.8%	100.0%
SP 100.0%	99.8%	100.0%

IHC		95% CI
SE 100.0%	97.9%	100.0%
SP 100.0%	99.8%	100.0%

Mahlum, et al., 2002

PCR		95.0% CI
PCR: Versus Virus Isolation in Serum		
SE 100.0%	75.0%	100.0%
SP 93.8%	87.2%	100.0%
PCR: Versus ELISA in Serum		
SE 100.0%	96.7%	100.0%
SP 87.2%	98.3%	99.5%
PCR: Versus Virus Isolation in Tissues		
SE 100.0%	96.7%	100.0%
SP 89.5%	98.3%	99.5%
PCR: Versus IHC in Tissues		
SE 97.3%	90.7%	100.0%
SP 90.5%	88.1%	93.0%

Figure 5. Representative test efficiency calculations taken from the literature. 95% confidence intervals are either assumed from the literture (95% CI?) or calculated, where possible (95% CI). Derived from literature sources as shown in table.

BVD diagnosis. Inclusion of commercial data is not meant to imply endorsement of any individual products.

Note that due to sample size limitations, what starts out appearing as excellent test efficiency measures ends up with quite wide 95% confidence intervals.

This is a common finding with published data and with data produced in advertising literature. We all need to be careful in depending on tests when we have only vague ideas as to their true potential efficiency.

Test cost

Another non-exhaustive, non-scientific sampling of six laboratories publishing their prices for tests on the internet (California, Guelph, Illinois, Missouri, Oklahoma, Wyoming) gave the following median prices for tests: ELISA, antibody = $15.00; ELISA, antigen = $13.65, IHC = $16.88; SN = $6.85; PCR = $25.50. Note this cost accounting does not include the costs of sample collection, identification, preparation, or transport. Also, be aware that the PCR tests all allowed pooling, generally up to five animals per test (lowering the potential cost/head to $5.10 on pooled samples).

Decision Processes/Thoughts on Testing for BVD in Herds

Before testing begins

One should not embark on a whole-herd BVD testing program lightly. As seen above it is a complex issue. However, if there is suspicion of a herd having had symptomatic animals, or has demonstrated otherwise non-diagnosed reproductive problems consistent with BVD, it is well worth the effort to start. In a 5-state survey for PIs in beef herds, Wittum, *et al*[19] found that cooperating veterinarians' classification of a herd as BVD 'suspect' (based on history/clinical signs) made the herd 5.8 times more likely to have PIs than randomly selected herds (95% CI on Odds Ratio = 1.4-34.1; EpiInfo 6.04/ Statcalc), though the proportional differences (10% vs 4%) were not found significant at the 5% level. Saliki, *et al*,[15] discovered that suspect individual animal cases of PIs or acute infections had a 10.5% likelihood of being viremic at testing, whereas non-suspect, general population cattle had a 1.9% individual likelihood of being viremic at testing. Needless to say, such figures are highly dependent upon the type and history of animals being tested, so we should not assume these figures represent the cattle in our own situations.

What to do at the start – screening a herd

Screening tests are designed, classically, to yield few false negatives, that is, to demonstrate a high sensitivity.[17] Diagnostic tests will be highly specific (i.e., low false positive rates), and will identify the true negatives within the tested group, and usually will show relatively poor sensitivity. However, there are trade-offs in any multi-test system. If the combination is to yield 'better' results, it depends on the relative merit of minimizing false positives at the expense of false negatives, or vice versa.[16] As shown in Figure 5, however, it appears there is little difference in the overall SEs and SPs of the various BVDV tests, putting a BVD program in a bit better standing than many clinical situations.

Test costs vary, as shown above. Balancing efficiency with total testing cost is important, but not a subject I can rationally approach here, because most overall testing costs will vary between herds, and averaging will be prone to over-interpretation. Suffice it to say that there are costs beyond just what the lab charges – and if those costs include potential damage or injury to animals, then those costs become exceptionally important. But even just looking at test costs, we can draw a few conclusions.

Stochastic partial budgeting for the testing decision – screening calves for antibodies

As an example of a decision tool we could use, I'll put forward one case of a stochastic partial budget for screening calves for antibodies, and will compare a herd where all the cows are BVD naïve against a herd where the cows are 70% immune to BVD. Partial budgets are the foundation decision support tool in economics.[16] A partial budget simply looks at the change in costs versus the change in revenues of a decision. A stochastic model is one in which at least one input is allowed to vary randomly. For our purposes, following with my comment about returns to programs being highly herd-specific, we

shall only look at testing costs – no attempt will be made to value the increases in revenue. The stochastic part of this model is that we will allow the SE and SP of the test to vary within the 95% confidence intervals defined in Figure 5 (using, in particular, the values from the top-most IDEXX ELISA antibody test; SE = 85-100%, SP= 93-100%) using over 100 simulations.

A lot of assumptions go into such a model, but for now let's see what happens without going into the assumptions in-depth. The herd size and pregnancy rates are taken from Wittum, *et al.*[19] The other numbers (exposure risks, risks of PI, etc.) are arbitrary assumptions.

The first 100 run scenario, as stated before, assumes none of the cows are immune to BVDV:

Note the '50th %' line (median values across 100 runs) for Model 1 in Figure 6. The median SE and SP are within 0.5% of the mid-point from the relevant test in Figure 5, and the minimum (MIN) and maximum (MAX) for each fits within the previously described confidence intervals. So, the stochastic part worked. What did it do? The median PVP was 55.6% (i.e., close to half the test positives were false positives), the median PVN was 99.6% – we had lots more confidence in negative antibody tests than in positive tests. This makes sense because the prevalence of titered calves (see outputs section of model) was low – 5%. Note also that the model falsely culled nearly four calves (FP = 3.9), and incorrectly returned about half a calf back to the herd as non-titered (FN = 0.4). Overall calving rate was 78% – definitely lower than desired. About 8% of calves turn out to be PIs in this model.

The second 100 run scenario, as stated above, assumes 70% of the herd is immune to BVDV:

In this model (Model 2; Figure 7) median PVP was nearly halved (28% vs 56%), and median PVN stayed about the same (both approximately 100%). This model still falsely culls nearly the same number of calves (3.5 vs 3.9), and returns one-quarter the number of false negatives back to the herd. Overall calving rates, not surprisingly, are improved by 12% (90% vs 78%), and the prevalence of PI calves is one-fourth that of Model 1 (2% vs 8%).

In a true herd situation, we could assign values to the extra calves saved, the higher calving rate, the lower risk of leaving positive animals in the herd and the lower prevalence of PI calves. We could also set up, fairly easily, the cost of a vaccination program to achieve a goal of 70% herd immunity, plus the added costs we'd incur by taking up BVDV biosecurity practices. With those values as inputs we could then determine just how much it is worth to this herd to correctly vaccinate the herd and practice good BVDV biosecurity. Then we would know whether this regimen is worthwhile or not.

Conclusions

BVDV, mostly because of its immunosuppressive nature, poses a great challenge to veterinary medicine. It is difficult to tease out its true effects on individual animals, let alone on an entire herd. It offers complexities in test execution and interpretation. As a result, we can rarely be fully confident in our test outcomes. But uncertainty does not absolve us of helping our clients make the most informed decisions possible – they have to live with the uncertain situations. By carefully documenting what we do know, and by then applying a

Inputs

149	cows in herd (avg herd size, Wittum)
89%	preg rate (preg rate, infected herds, Wittum)
0%	cows immune (assumption)
50%	exposure to BVDV (assumption)
50%	exposure occured at 60-120 da gestation (assumption)
50%	risk of PI, given exposure (assumption)
25%	risk of PG loss, given exposure (assumption)
5%	baseline PG wastage rate (assumption)
33%	prob of non-PI fetus mounting titer, if exposed (assumption)

Model 1 - Naive herd

Calculations

132.61	preg cows
132.61	preg cows at risk
66.3	preg cows exposed to BVD
33.2	preg cows exposed at 60-120 da gestation
16.6	PI calves
8.3	PI abortions/losses
8.3	PI calves born

99.5	non-BVD pregnancies
5.0	baseline PG wastage rate
94.5	normal, non-BVD calves born
5.2	normal, non-BVD calves born with titers

Outputs

102.8	total calf crop
78%	calving %
8%	PI prevalence in calves
5%	Prevalence of calves with titers

	SE	SP	PVP	PVN	FPR	FNR	TP	TN	FP	FN
count	100	100	100	100	100	100	100	100	100	100
min	85.0%	93.0%	39.6%	99.2%	15.8%	0.0%	4.4	90.7	1.0	0.0
max	100.0%	100.0%	84.2%	100.0%	60.4%	0.8%	5.2	96.6	6.8	0.8
25th%	90.0%	94.0%	45.2%	99.4%	28.1%	0.2%	4.7	91.7	2.0	0.2
50th%	93.0%	96.0%	55.6%	99.6%	44.4%	0.4%	4.8	93.7	3.9	0.4
75th%	97.0%	98.0%	71.9%	99.8%	54.8%	0.6%	5.0	95.6	5.9	0.5
avg	93.09%	96.08%	59.15%	99.62%	40.85%	0.38%	4.84	93.75	3.82	0.36
std	4.29%	2.07%	14.66%	0.24%	14.66%	0.24%	0.22	2.02	2.02	0.22

Figure 6. Stochastic partial budget model of a BVDV naive cow-calf herd being exposed when many of the cows were at the riskiest stage of gestation for PI generation.

Inputs

149	cows in herd (avg herd size, Wittum)
89%	preg rate (preg rate, infected herds, Wittum)
70%	cows immune (assumption)
50%	exposure to BVDV (assumption)
50%	exposure occured at 60-120 da gestation (assumption)
50%	risk of PI, given exposure (assumption)
25%	risk of PG loss, given exposure (assumption)
5%	baseline PG wastage rate (assumption)
33%	prob of non-PI fetus mounting titer, if exposed (assumption)

Model 2 - 70% herd immunity

Calculations

132.61	preg cows
39.783	preg cows at risk
19.9	preg cows exposed to BVD
9.9	preg cows exposed at 60-120 da gestation
5.0	PI calves
2.5	PI abortions/losses
2.5	PI calves born

122.7	non-BVD pregnancies
6.1	baseline PG wastage rate
116.5	normal, non-BVD calves born
1.6	normal, non-BVD calves born with titers

Outputs

119.0	total calf crop
90%	calving %
2%	PI prevalence in calves
1%	Prevalence of calves with titers

	SE	SP	PVP	PVN	FPR	FNR	TP	TN	FP	FN
count	100	100	100	100	100	100	100	100	100	100
min	85.0%	93.0%	13.9%	99.8%	43.0%	0.0%	1.3	109.2	1.2	0.0
max	100.0%	100.0%	57.0%	100.0%	86.1%	0.2%	1.6	116.3	8.2	0.2
25th%	88.8%	94.0%	16.8%	99.8%	61.5%	0.0%	1.4	110.4	2.3	0.0
50th%	92.8%	96.2%	28.0%	99.9%	72.0%	0.1%	1.4	113.9	3.5	0.1
75th%	97.0%	98.0%	38.5%	100.0%	83.2%	0.2%	1.5	115.1	7.0	0.2
avg	92.65%	96.17%	30.09%	99.90%	69.91%	0.10%	1.44	112.96	4.50	0.11
std	4.64%	2.17%	14.51%	0.06%	14.51%	0.06%	0.07	2.55	2.55	0.07

Figure 7. Second stochastic partial budget model for BVDV infection of a cow-calf herd. Here, however, 70% of the cow-herd is immune at time of exposure.

formal decision process based on biology and economics, we can achieve means to wind our way through the issue of testing herds for BVDV.

References

1. Anderson BB: Is your herd BVD free? *Angus* 51-52, 2001.
2. Bezek DM: Screening of cattle herds for persistent BVDV infections. *Large Animal Pract* 20(3): 10-14. 1999.
3. Brock KV: Pathogenesis of BVDV infections. Auburn University Bovine Virus Diarrhea Website. <www.vetmed.auburn.edu/~brockkv/path.htm> Accessed April 2003. 2003a.
4. Brock KV: Prevention and control of BVDV. Auburn University Bovine Virus Diarrhea Website. <www.vetmed.auburn.edu/~brockkv/prevcont.htm> Accessed April 2003. 2003b.
5. Broderson B, Smith DR, Steffen DJ: Immunohistochemistry on skin biopsies for bovine viral diarrhea virus as a test for persistent infection. University of Nebraska Veterinary Diagnostic Laboratory / North Dakota State University Extension Newsletter, 3rd Qtr 2000. [accessed via Pennsylvania State University Veterinary Science Extension website] <www.vetsci.psu.edu/Ext/Newsletters/Diagnostic/Vn07011.htm>. 2000.
6. Cortese VS, Grooms DL, Ellis J, Bolin SR, Ridpath JF, Brock KV: Protection of pregnant cattle and their fetuses against infection with bovine viral diarrhea virus type 1 by use of a modified-live virus vaccine. *Am J Vet Res* 59: (11) 1409-1413, 1998.
7. Cree J: BVDV - Type II. Western Dairyman. Accessed April 2003 at UC Davis Veterinary Medicine Extension website <www.vetmed.ucdavis,edu/vetext/INF-DA/INF-DA_BVDV.HTML>
8. Fleiss JL: Statistical methods for rates and proportions, 2nd ed. John Wiley & Sons, Inc. New York, 1981.
9. Lindberg A, Groenendaal H, Alenius S, Emanuelson U: Validation of a test for dams carrying foetuses persistently infected with bovine viral-diarrhoea virus based on determination of antibody levels in late pregnancy. *Prev Vet Med* 51: 199-214, 2001.
10. IDEXX Corp: Quantitative measurement of antibodies to Bovine Viral Diarrhea Virus. [IDEXX *HerdChek*® advertising supplement] <www.idexx.com> 2003.
11. Ishmael S: Things you should know about ... BVD. *The Cattleman*. LXXVI: (6): 40-50, 1999.
12. Mahlum CE, Haugerud S, Shivers JL, Rossow KD, Goyal SM, Collins JE, Faaberg JE: Detection of bovine viral diarrhea virus by TaqMan® reverse transcription polymerase chain reaction. *J Vet Diagn Invest* 14:120-125, 2002.
13. Martin SW, Meek AH, Willeberg P: *Vet Epidemiology*. Iowa St Univ Press, Ames, IA, 1987.
14. Pennsylvania State Veterinary Science Extension: Bovine Virus Diarrhea. Veterinary Science Information Series. May 2000.
15. Saliki JT, Fulton RW, Hull SR, Dubovi EJ: Microtiter virus isolation and enzyme immunoassays for detection of bovine viral diarrhea virus in cattle serum. *J Clin Micro* 35: 803-807, 1997.
16. Slenning BD: Quantitative tools for production-oriented veterinarians. in: Radostits OM (ed). *Herd Health: Food Animal Production Medicine*, ed 3. WB Saunders & Co., Philadelphia, PA, 2001.
17. Smith RD, Slenning BD: Decision analysis: dealing with uncertainty in diagnostic testing. *Prev Vet Med.* 30 (45) (1-2):139-162, 2000.
18. Vaughn M: SN titer response comparisons among fourteen diagnostic laboratories for antibodies protecting against IBR, BVD, and BRSV virus following the administration of modified live vaccine to weaning age calves. *Proc Am Assoc Bov Pract* 30: 141-143, 1997.
19. Wittum TE, Grotelueschen DM, Brock KV, Kvasnicka WG, Floyd JG, Kelling CL, Odde KG: Persistent bovine viral diarrhoea virus infection in US beef herds. *Prev Vet Med* 49: 83-94, 2001.