ABSTRACT
To understand the rationale behind recommended control programs for liver flukes in cattle, the economic impact and the complex life cycle of *Fasciola hepatica* need to be appreciated. Fluke-infected cattle rarely demonstrate clinical disease, but subclinical impairment of feed efficiency, growth, and fertility can have an important impact on productivity. Although the precise benefit from controlling liver flukes is unknown due to the inherent variability between studies, most investigations demonstrate a considerable economic advantage to treatment. In addition, recent studies have demonstrated that liver flukes may cause a decrease in host fertility by altering normal metabolism and/or balance of sex hormones. This review focuses on these issues and how to best use available drugs to implement optimal fluke control programs.

INTRODUCTION
Current recommendations for the control of liver flukes (*Fasciola hepatica*) in cattle are based on strategically timed treatments with flukicidal drugs. The optimal timing of these treatments has been determined by studying the seasonal transmission dynamics of liver flukes in numerous locations throughout the world. Because of the long time required to complete the fluke life cycle, the window of opportunity to administer strategic treatments and still receive meaningful benefit is fairly large. To properly understand the rationale behind recommended control programs, reasonable deviations that can be made from these recommendations, and issues pertaining to the economic impact of fluke infections in cattle, the complex life cycle of liver flukes (Figure 1) needs to be appreciated.

Liver fluke transmission is dependent on the presence of its snail intermediate host; therefore, the distribution of the parasite is limited to geographic areas where the appropriate snail species is present. In the US, liver flukes are enzootic primarily in the Gulf coast and western states, where high annual rainfall, large areas of poorly drained pasture, and certain soil types provide suitable lymnaeid snail habitats. In addition, use of irrigated pastures, which is common in the western US, may increase the distribution and prevalence of liver flukes. Therefore, control of liver flukes is relevant only in areas where the parasite is enzootic or when cattle are purchased from such areas. This situation is somewhat different from that of gastrointestinal nematodes, where control is almost always an important aspect of bovine health programs in virtually all cattle-producing areas of the US.

Adult liver flukes (Figure 2) reside in the bile ducts of host animals, and eggs are passed onto...
the pasture in the feces. After a short period of development (usually 2 to 3 weeks), a miracidium hatches from the egg and attempts to find and penetrate a snail intermediate host. The parasite develops and replicates asexually in the snail over many weeks. Under optimal conditions, parasite maturation within the snail to the cercarial stage takes approximately 5 to 7 weeks, and a single miracidium can develop into several hundred cercariae. Under wet conditions, cercariae emerge from the snail and swim until they find and attach to vegetation. The cercariae then shed their tails and secrete a protective coat, forming the encysted infective stage called metacercariae. Cattle become infected primarily by ingesting the metacercarial cysts on forage, but they also can become infected by ingesting cysts suspended on soil and detritus while drinking contaminated water. The length of time that metacercariae survive on pasture primarily depends on available moisture. Under the hot and dry pasture conditions of coastal Texas during the summer, metacercariae were rapidly killed; however, under conditions of high humidity, such as in Louisiana during the summer, metacercariae may survive for extended periods.

Once ingested by a ruminant host, the metacercariae excyst, releasing juvenile flukes. The juvenile flukes penetrate the wall of the small intestine, migrate through the peritoneal cavity over a week’s time, and then penetrate through the liver capsule. Juvenile flukes migrate through the hepatic parenchyma for approximately 6 to 8 weeks before entering the bile ducts where they mature. Egg production can begin as early as 8 weeks after infection; however, most infections do not become patent until after approximately 11 to 12 weeks. Thus, completion of the entire parasite life cycle, from the time an egg is shed onto pasture until a newly infected animal reinfects the pasture with the next generation of fluke eggs, generally requires 18 to 24 weeks (4.5 to 6 months).
Although the life cycle of *F. hepatica* does not change, seasonal transmission profiles differ for each geographic region. Therefore, in order to gain maximum benefit from treatment, fluke control programs must be designed based on knowledge of local parasite transmission patterns. In addition, such management-related factors as age and use-class of cattle, stocking rate, nutritional status, environmental stresses, and concomitant infection with gastrointestinal nematodes play an important role in determining the immune status of cattle and the ensuing risk of infection and economic loss. Only three flukicidal products are available for use in the US market, and all are extremely limited in their ability to kill the migrating stage of *F. hepatica* younger than 8 weeks. Only one product has >90% efficacy against the 8- to 12-week-old immature fluke, whereas the other two products kill only adult flukes with high efficacy. Therefore, timing and frequency of treatments must be based on economic considerations. This review will focus on economic considerations so that the rationale behind strategic drug treatment can be properly understood. In addition, current knowledge regarding the economic impact of liver flukes in stocker, cow-calf, and feedlot cattle will be briefly reviewed.

### CLINICAL SIGNS AND PATHOLOGY

On a herd basis, clinical signs of fluke infection are usually vague (i.e., reduced productivity) and can be difficult to discern from the effects of less-than-optimal management or other chronic disease conditions. From a clinical standpoint, bovine fascioliasis generally can be considered a subclinical disease. When extremely high fluke burdens rapidly accumulate, however, outbreaks of acute or subacute bovine fascioliasis can occur. In these situations, clinical disease is caused by extensive damage to the hepatic parenchyma produced by migrating juvenile flukes. Alternatively, chronic disease results from a combination of the partially resolved hepatic damage that follows the acute phase and the blood sucking activities of the adult flukes within the bile ducts. Clinical disease resulting from chronic infection is uncommon in cattle; it is most frequently seen in cattle younger than 2 years and is characterized by weight loss, anemia, hypoproteinemia, eosinophilia, general depression, and occasionally death. In response to the traumatic injury caused by the migrating flukes, tracts of coagulative necrosis develop, which result in a diffusely fibrotic hepatic parenchyma containing hemorrhagic streaks and foci. These lesions can predispose cattle to black disease (infectious necrotic hepatitis) and bacillary hemoglobinuria due to *Clostridium novyi* and *C. haemolyticum*, respectively. In the bile ducts, the adult flukes produce a mechanical irritation that causes cholangiohepatitis. This leads to dilation, thickening, and extensive fibrosis of the duct wall, resulting in stenosis and calcification (Figure 3).
HOST IMMUNITY
Over time, cattle may develop a partially protective immune response to *F. hepatica*. The interaction of such factors as age of the host, innate resistance of the host, previous exposure of the host, and present level of parasite exposure determine the degree of parasite establishment and the pathologic impact of the infection. Older cattle with previous exposure have a greater resistance to infection than do young parasite-naive calves. In addition, flukes are gradually eliminated so that most flukes acquired during the major transmission period of 1 year are lost before the same time the next year. Because acquired immunity is only partially protective, however, cattle remain susceptible to reinfection each year.

EFFICACY OF AVAILABLE FLUKICIDES
Only two drugs (marketed as three products) are available in the US for the treatment of liver flukes: clorsulon (Curatrem®; Merial, Iselin, NJ); clorsulon plus ivermectin (Ivomec®-Plus; Merial, Iselin, NJ); and albendazole (Valbazen®; Pfizer Animal Health, Exton, PA; Table 1). Clorsulon (administered orally as a drench at a dosage of 7 mg/kg) has the best efficacy against adult stages (>99%) and also kills immature flukes (8 to 12 weeks) with fairly high efficacy (85% to 95%)⁹-¹¹; however, clorsulon only kills flukes and has no effect against other parasites. The combination product of clorsulon plus ivermectin (2 mg/kg clorsulon, 0.2 mg/kg ivermectin; administered subcutaneously) has approximately 97% to 99% efficacy against adult flukes¹¹-¹³ but is not very effective against immature stages.⁹ This lower efficacy as compared with the oral drench form is because of the lower clorsulon dose (2 mg/kg) in the subcutaneous formulation; however, the addition of ivermectin to clorsulon makes this a broad-spectrum product that will kill nematodes and ectoparasites in addition to adult liver flukes. Albendazole is a broad-spectrum product, administered by oral drench, which kills adult liver flukes, nematodes, and cestodes. At the labeled dosage (10 mg/kg), the efficacy of albendazole against adult flukes is variable (76% to 92%) and the efficacy against immature stages is poor.¹¹,¹⁴,¹⁵ At higher doses (≥15 mg/kg), however, the efficacy of albendazole approaches that of clorsulon.¹⁶

None of these three flukicidal products can kill the migrating juvenile stage (<8 weeks of age); therefore, the limited efficacy of these

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### TABLE 1. Comparison of Flukicidal Drugs Currently Available in the US

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clorsulon</th>
<th>Clorsulon + Ivermectin</th>
<th>Albendazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/kg)</td>
<td>7</td>
<td>2 (0.2)</td>
<td>10</td>
</tr>
<tr>
<td>Kills Adult Flukes</td>
<td>Yes (99%)</td>
<td>Yes (97%)</td>
<td>Yes (76%)</td>
</tr>
<tr>
<td>(8–12 weeks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kills Immature Flukes*</td>
<td>Yes (85%)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Kills Juvenile Flukes (0–8 weeks)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Oral drench</td>
<td>Subcutaneous injection</td>
<td>Oral drench</td>
</tr>
<tr>
<td>Kills Nematodes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Kills Cestodes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Kills Ectoparasites</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*See text for references regarding drug efficacy.
drugs against juvenile and immature stages of *F. hepatica* must be considered when making decisions regarding the timing of treatments. When treating at a time of year when most flukes would be expected to be mature, all three products have fairly high to very high efficacy. If treating during a period of the year when active transmission is occurring, however, clorsulon given orally is the drug of choice because of its labeled efficacy against immature 8- to 12-week-old flukes. In certain other instances, choosing clorsulon may be justified because of its higher efficacy.

Several other flukicidal drugs with efficacy against the migrating juvenile and immature bile duct stages are approved and available for use in some countries outside the US. Tri-clabendazole removes all developing stages older than 1 week, and rafoxanide, closantel, and nitroxinil remove all developing stages older than 4 weeks. Where these drugs are available, control strategies differ because it is not necessary to wait until flukes mature before using these drugs.

**ECONOMIC IMPORTANCE**

When cattle become clinically ill as a result of a parasitic infection, the economic ramifications are clear. However, clinical disease is uncommon and cattle tend to harbor parasitic infections that are clinically unapparent. Although infected cattle may not appear ill, subclinical parasitic infections are recognized as causing economically important reductions in animal productivity. Economic losses from liver flukes may result directly from increased liver condemnations at slaughter and indirectly from decreased livestock productivity. Although direct losses are easier to measure, indirect losses are considered to be far more economically important. Beef producers are affected by increased culling of cows, reduced sale weights of culled cows, lowered reproductive performance in the brood cow herd, reduced calf weaning weights, and reduced rates of growth in stockers. Economic losses in feedlots result from reduced feed-conversion ratios and lowered average daily gains, and fluke-infected dairy cows produce less milk. Precise economic benefits of liver fluke control are difficult to quantify because of interactions among physiologic, nutritional, associated disease, and climatic/geographic factors. Interaction among these factors causes tremendous variation in pasture infectivity and the physiologic consequences of infection from year to year and ranch to ranch. These factors, combined with differences in experimental design, cause a great deal of variation between studies regarding the benefits of liver fluke control. Most studies do, however, demonstrate a benefit to fluke control, and differences between studies are mostly a matter of magnitude in the level of benefit. Although there are a few published studies that failed to demonstrate any economic impact of fluke infections in cattle, review of the available literature suggests that the economic benefits of controlling liver flukes are substantial. The following is a brief review of some of the studies investigating the effects of liver flukes on cattle performance.

**Economic Analyses**

Data obtained from a large survey of cattle producers in Florida showed that specific benefits from control of liver flukes through appropriate treatment of cattle included 18- to 22-lb heavier cull cows, 1% to 3% more calves, and 30- to 45-lb heavier calves at weaning, yielding a net return to the producer of $15.19 to $31.03 per brood cow, depending on size of the calf crop and calf prices. A separate economic analysis of liver fluke control in Florida reported benefit–cost ratios ranging from 4:1 to 16:1 depending on the number of treatments given and the range of estimates includ-
ed in the analysis of production parameters.20 These types of studies provide useful data, but it needs to be understood that these values are only estimates based on economic assumptions and are not based on controlled scientific studies with fluke-infected cattle.

**Cow–Calf Study**

In a study conducted at a commercial cow–calf operation in Louisiana, calves from cows receiving treatments for both flukes and nematodes had an average weight gain advantage of 19.6 lb in 205-day adjusted weaning weights compared with that of calves from cows receiving treatment for nematodes only.1 Because all treatment groups were maintained on the same pasture, it was suggested by the authors of this study that administration of flukicides to cows had a positive effect on productivity by increasing milk production, resulting in heavier calves. In a Florida study also conducted on a large commercial cow–calf operation, treatment of cows for liver flukes exhibited a positive net economic return regardless of the price of calves.23

**Stocker/Replacement Heifer**

In a 4-year study of beef replacement heifers in Louisiana, the combination of nematode and fluke infections had a cumulative negative effect on weight gain.24 Heifers receiving treatments for both nematodes and flukes had a significantly increased weight gain compared with that of heifers receiving treatment for only nematodes or flukes. Heifers receiving both treatments also had a significantly increased pregnancy rate compared with that of control heifers receiving no treatments. These results support the common observation that infections with numerous parasite species have a cumulative effect on host animals. A European study in which weaned calves (8 to 9 months old) were experimentally infected with liver flukes demonstrated that subclinical infections (averaging 54 flukes per calf) cause a reduction in weight gains by 8% during the first 6 months of infection. Higher levels of infection (average of 140 flukes per calf) reduced weight gain by 29% and caused the appearance of clinical signs in some animals.19 Another European study that examined the effect of fluke infection on feed consumption, growth, and fertility, showed that heifers infected with subclinical fluke burdens grew more slowly and had both a lower feed efficiency and a lower conception rate.25

**Feedlot**

Feedlot studies performed in several fluke enzootic states in the southern US demonstrated a mean increase of 9.5% in average daily gains when fluke-infected cattle were treated with albendazole.1 A feeding trial performed in an Oklahoma feedlot demonstrated that fluke-infected cattle gained 5.9% less than did their uninfected pen mates during 135 days of feeding, resulting in a reduction of 19 lb in mean carcass weight.26 In 40 pens of cattle, the incidence of fluke infection in individual pens varied from 0% to 75%. When incidence of fluke infection was correlated with production parameters, it was found that pen daily gains and pen dry matter intake both decreased as the incidence of flukes for that pen increased.

Another study used a design where cattle were experimentally infected with a low number of flukes, grazed on fluke-free pasture, and then treated with either ivermectin or ivermectin/clorsulon 10.5 weeks later, before entering the feedlot.27 In theory, at 10.5 weeks after infection, many flukes would still be immature and not fully susceptible to this treatment. This assumption was confirmed at slaughter when ivermectin/clorsulon-treated cattle still had approximately 50% as many flukes as did cattle treated with ivermectin
only. Although no differences were detected between fluke-infected and uninfected cattle during the immature fluke/grazing stage, in the feedlot phase, cattle that received the flukicide (ivermectin + clorsulon) demonstrated a significant improvement in both average daily gain and total gain compared with cattle receiving ivermectin only.

**FERTILITY**

It has long been reported that infection with liver flukes reduces animal fertility. It was unknown, however, whether this effect was a general consequence of reduced well-being and retarded growth or whether the parasites were somehow affecting hormonal balance. Although few published studies have investigated this issue, mounting evidence suggests that liver flukes do affect sex hormone balance and metabolism. In 1986, a study on peripuberal rams suggested that infection with liver flukes impairs hepatic catabolism of androgen. Similar results were described in a study using a rat model in which liver fluke infection caused a significant decrease in hepatic P-450–dependent metabolism of progesterone and testosterone. A recent study on prepuberal heifers demonstrated a significant delay of 39 days in the onset of first estrus in fluke-infected animals. Fluke-infected heifers also had significantly higher levels of estrogen and significantly lower levels of progesterone than did uninfected animals. The cause of this effect is not clear, but evidence suggests that liver flukes somehow alter normal metabolism and/or balance of sex hormones. Based on these data, prebreeding treatment in addition to yearly strategic treatment for flukes may be justified if cattle are being pastured where flukes are a significant concern.

**FLUKE EPIDEMIOLOGY AND TREATMENT RECOMMENDATIONS**

The available data are fairly convincing that productivity is reduced in cattle infected with liver flukes. Given the complexity of the epidemiology of this parasite, how are flukicide drugs best used to improve cattle performance? Recommendations are twofold: (1) use strategic treatment to reduce pasture infectivity so that cattle will become infected with fewer parasites in the upcoming months, and (2) use treatment to kill flukes and improve the immediate performance of cattle. Properly timed strategic treatment will accomplish both goals. Implementation of a strategic control program is the best approach, especially for cow–calf operations, for avoiding infection with economically important parasite burdens. To make sound decisions regarding the economic benefits of fluke treatment, managers and veterinarians of stocker and feedlot cattle need to know the source of the animals and consider the time of year.

Current recommendations for fluke control on the Gulf coast of the US are for cattle to be treated with a flukicide once annually in the late summer or early autumn with an optional spring treatment based on local parameters of risk. Treatment is best given in the late summer (September) in Florida and in early autumn (October through November) in the other Gulf states (Figure 4). The rationale for this treatment plan is that fluke transmission ceases during summer because snail intermediate hosts burrow into the mud and aestivate, thus contamination of the pasture with metacercariae ceases. Metacercariae shed in the spring are killed by the heat in summer and are not replaced after snails enter summer aestivation. Thus, flukes are presumed to survive the summer only as adult flukes in the livers of cattle. Treatment of cattle with flukicides in the late summer/early autumn prevents the shedding of large numbers of fluke eggs onto pasture when the essentially fluke-free snails emerge from summer aestivation with the onset of
cooler weather. Because newly emerged snails and their subsequent offspring are not likely to become infected if cattle have been treated in the preceding month, fluke transmission to cattle is greatly reduced during the following winter and spring. As an added benefit, virtually all flukes in cattle in the autumn will be mature adults and therefore fully susceptible to flukicides.

Treatment in the spring is optional because its purpose is to reduce fluke burdens carried over the summer by cattle during high-risk years or on high-risk properties. Spring treatment is primarily palliative rather than curative because many flukes are immature and thus not susceptible to flukicides. Because many flukes survive spring treatment, it should be given in addition to, but never in place of, a late summer/early autumn treatment. In a study on fluke epidemiology in Florida, it was observed that ranches using once yearly strategic treatment in the early autumn had greatly reduced infection prevalence in their herds compared with ranches that did not treat at that time. Of seven ranches studied, the one ranch that treated only in the spring had the highest herd prevalence and the highest fluke egg counts.

In the cool, temperate northwestern US, fluke transmission ceases in December because temperatures are too low for parasite development and cattle are frequently removed from pasture. Because most fluke transmission occurs from August to November, a single treatment should be given in the late winter or early spring, preferably before turnout to spring pasture, when all flukes are mature and fully susceptible to flukicides (Figure 5). Eliminating flukes from cattle at this time will minimize contamination of pasture with eggs when cattle are replaced to pasture and snail populations return. Infected snails, metacercariae, and eggs rarely survive the winter and do not seem to have an important epidemiologic role in fluke transmission in northwestern states. Autumn treatment has little benefit because most flukes are immature and not susceptible to flukicides. In northwestern states with warmer winters, fluke transmission has not been well studied.

Recommendations for treatment at a specific time of the year are for optimal parasite control; however, the period when treatment will achieve a health/economic benefit is probably much longer. On the Gulf coast, delaying

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Figure 4. Schematic representation of liver fluke epidemiology for Gulf coast states (see text for differences between Florida and other states).

- Treatments Fully Effective: Virtually 100% of flukes infecting cattle are mature adults and therefore fully susceptible to flukicidal drugs.
- Optimal Treatment: Period when virtually 100% of flukes infecting cattle are mature adults and there are no or very few snail intermediate hosts on pasture.
- Minimal Gain from Treatment: Most flukes are in the juvenile and immature stages. Clorsulon will kill immature flukes, but none of the drugs will kill the juvenile stage. Treatment is probably not economically justified.
- Treatments Not Completely Effective: Flukes infecting cattle will be at all stages of development. Because clorsulon will kill the immature stages as well as the adults, it is the drug of choice when treating during this time; however, the juvenile flukes will not be killed and retreatment in the late summer/autumn is recommended.

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Seasonal Incidence and Recommended Treatment of Liver Flukes in Cattle in the Southeastern United States

- Immatures
- Immatures & Adults
- Adults
- Months

Figure 4. Schematic representation of liver fluke epidemiology for Gulf coast states (see text for differences between Florida and other states).
treatment until late autumn will reduce the benefit of treatment because more snails will become infected, leading to greater transmission in the winter and early spring as snail populations increase. In addition, poor cow nutrition and increased transmission of *Ostertagia* occur in winter on the Gulf coast. The combination of nutritional stress and infection with *Ostertagia* exacerbates the health and economic consequences of untreated fluke infections. Although cattle should be treated in early autumn, high drug efficacy and significant economic benefit will probably still be achieved if treatment is given before December.

**CONCLUSION**

Bovine fascioliasis is generally considered a subclinical disease with economic losses resulting primarily from decreased animal productivity. Several economic analyses and studies with fluke-infected cattle have demonstrated an economic benefit to control. However, control of *F. hepatica* is complicated by the lack of available drugs (in the US) with efficacy against parasites younger than 8 weeks and by the complexity of the parasite’s life cycle and epidemiology. Because flukes younger than 8 weeks cannot be killed, control programs are primarily aimed at preventing contamination of pastures with infective stages and subsequent transmission to cattle is the basis of most treatment recommendations. Although there are optimal times for treatment that vary with geographic region, beneficial treatment can occur over a longer period. *F. hepatica* is an important parasite of cattle, and control programs based on an understanding of the parasite’s life cycle and epidemiology can significantly increase the productivity of cattle.

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**Figure 5.** Schematic representation of liver fluke epidemiology in the northwestern US in regions with cold winters.

- **Treatments Fully Effective:** Virtually 100% of flukes infecting cattle are mature adults and therefore fully susceptible to flukicidal drugs.
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REFERENCES


