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Vaccines for preventing enterotoxigenic *Escherichia coli* infections in farm animals

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Fimbrial vaccines are routinely given parenterally to pregnant cattle, sheep and swine to protect suckling newborn calves, lambs and pigs against enterotoxigenic Escherichia coli *(ETEC) infections. Such vaccines are practical and effective because (1) most fatal ETEC infections in farm animals occur in the early neonatal period when the antibody titres in colostrum and milk are highest; (2) more than 90% of the ETEC in farm animals belong to a small family of fimbrial antigen types; (3) fimbriae consist of good protein antigens on the bacterial surface where they are readily accessible to antibody; (4) fimbriae are required for a critical step (adhesion-colonization) early in the pathogenesis of the disease. ETEC infections continue to be a significant clinical problem in farm animals in spite of extensive use of fimbriae-based vaccines. Definitive data on the efficacy of the commercial vaccines in field use are not available. The prevailing perception among animal health professionals is that the vaccines are effective, that the problem occurs chiefly among non-vaccinated animals, and that in some herds vaccination moves peak prevalence of disease from the first to the second or third week after birth, when mortality is lower. It has been suggested that extensive use of vaccines will rapidly select for the emergence of novel or previously low prevalence fimbrial antigen types. There is no evidence that this has happened after a decade of routine vaccine use in the United States. However, there is no active direct surveillance for such emergence. In contrast to the rational development of vaccines to provide passive lacteal protection against ETEC in suckling neonates, comparatively little progress has been made in providing the knowledge required for development of vaccines to protect against postweaning ETEC infections in swine.*

Keywords: Vaccines; enterotoxigenic *E. coli*; fimbrial; animals; United States

INTRODUCTION

Research conducted in animal and human health laboratories around the world from 1960–1980 established the rationale for vaccines to control enterotoxigenic *Escherichia coli* (ETEC) infections in neonatal farm animals. Comprehensive reviews of that research are available[1–12]. The research confirmed the long-held hypothesis that certain strains of *E. coli* caused a diarrhoeal disease (colibacillosis) which occurred commonly among neonatal calves, pigs, and lambs[13–16]. It establishes the concepts that:

- the pathogenesis of diarrhoea caused by ETEC is similar to human cholera (bacteria adhere to small intestinal epithelium and stimulate local secretion of electrolytes and water)
- *E. coli* enterotoxins and specific types of fimbriae (pili) are required virulence attributes of ETEC which act, respectively, as intestinal secretagogues and adhesins (colonization factors)
- host species specificity of ETEC depends largely on the ligand–receptor fit among various types of fimbriae and receptors on the intestinal epithelial cells of the host
- more than 90% of the ETEC associated with disease in animals belong to a small family of fimbriae and enterotoxin types
- most fatal ETEC infections in farm animals occur in the early neonatal or suckling period
- neonates suckling dams vaccinated with ETEC fimbriae are protected against challenge by ETEC bearing fimbrial antigens homologous to the vaccine strain.

General acceptance of these concepts led to the commercial development of fimbriae based vaccines to control ETEC infections in farm animals. Most of the vaccines are designed for parenteral administration to pregnant dams to increase the content of fimbrial antibody in colostrum and milk. Suckling establishes and maintains a level of fimbrial antibody in the small intestine to prevent intensive colonization by ETEC during the highly susceptible neonatal period.

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COMMERCIAL VACCINES IN THE UNITED STATES

The first fimbriae-based ETEC vaccine (bacterin) for commercial use in US livestock was licensed by the United States Department of Agriculture (USDA) in 1980. Such vaccines (bacterins) have now been in routine use in the US for about ten years. We describe here some aspects of the use of ETEC vaccines in the US. We will also attempt to assess what impact, if any, this decade of routine use of fimbriae based vaccines has had on the disease in the US.

Data on USDA licensed biologicals produced for the prevention of *E. coli* infections in livestock during 1990 and 1991 are summarized in *Table 1*. In 1991, 32 distinct commercial vaccines (bacterins) were produced for the parenteral vaccination of pregnant cattle, sheep, and swine. The vaccines for use in cattle all included fimbrial antigen F5 (K99), while those for swine all included F4 (K88), F5 and F6 (987P). Twenty-one of the vaccines also included F41, and at least one included the F1 (type 1 pili) fimbrial antigen. In addition to fimbrial antigens, one of the swine products (vaccines) includes a label claim for the heat labile enterotoxin based on the B subunit (LT_B) of the toxin used as antigen. Four of the vaccines were produced from *E. coli* strains containing plasmids constructed via recombinant DNA technology. Many of the products were designed to protect against other diseases in addition to ETEC infection. Therefore, in addition to ETEC fimbrial antigens, two-thirds of the vaccines produced also contained antigens from other pathogens (Pasteurella sp., Bordetella sp., Clostridium sp., rotavirus, and coronavirus). Most of the products were designed for parenteral vaccination with two doses during the first pregnancy and a single booster during each succeeding pregnancy. Most (63%) of the 26.8 million doses produced during 1991 were for use in swine, with 37% produced for cattle and minor use in sheep. The estimated inventories of livestock on US farms during 1990–91 were 7.7 million female breeding swine and 43.7 million breeding cows (10.1 million dairy and 33.6 million beef)[17]. Most breeding female swine farrow about twice a year and remain in the breeding herd for about 2 years. Most cows calve once a year and remain in the breeding herd for five years or longer. Thus, saturation use of the vaccines in the US swine and cattle breeding herds would probably require an annual production of about 19 and 50 million doses, respectively. Assuming that most of the vaccine produced in the US is used domestically (some is exported, but the amount is not known) and that the number of doses produced/year approximates the number of doses used/year, then the US animal inventory data combined with the vaccine production data in *Table 1* indicates that the vaccines are used much more intensively in swine than in cattle. Intensive use in pregnant swine is confirmed by a recent survey in which 47% of US swine producers reported routine use of *E. coli* vaccines[18].

Table 1 United States Department of Agriculture licensed biological products marketed for prevention of *E. coli* infection in livestock – 1990 and 1991

	Number of products		Doses (millions)	
Biological	1990	1991	1990	1991
Vaccines[a]				
Swine[b]	23	23	14	17
Cattle/Sheep[c]	10	9	9	10
Total	33	32	23	27
Antiserum[d]	9	12	5	8

[a]Bacterins
[b]Includes three vaccines with label claims for use in both cattle and swine
[c]Includes one vaccine with a label claim for use in sheep
[d]For oral and parenteral use in calves, lambs, pigs, foals

The prevalence and severity of clinical ETEC infections is greatest under intensive management systems (close confinement of large numbers of animals). Most beef cows in the US are managed extensively, while intensive management systems are common in dairy and swine production. Thus, we think that the vaccines are probably used in a greater proportion of dairy than beef cows. It has been recommended that the vaccines be used strategically rather than universally in cattle[1]. A cost:benefit ratio of 5.9 was achieved in a study of the economic aspects of such strategic use[1].

In addition to the vaccines, nearly 8 million doses of *E. coli* antiserum were produced during 1991 (*Table 1*). These products are designed for oral or parenteral administration to newborn calves, lambs, piglets, or foals. Some of these products are designed to protect against *E. coli* bacteraemia and septicaemia in hypogammaglobulinaemic neonates. Hypogammaglobulinaemia is common because there is normally no passive Ig transfer *in utero*, and transfer under farm or ranch conditions is frequently inadequate. Several of the orally administered products contain antibody against fimbriae and are designed to prevent ETEC infections. This approach is rational because a high proportion of fatal ETEC infections occur during the first few days after birth. This is particularly so in calves because nearly all calf ETEC produce F5 fimbriae, and calves are only susceptible to colonization by $F5^+$ ETEC during the first one or two days after birth[1,15]. Thus, a few hours of local protection delivered to the intestine by a single oral dose of F5 monoclonal antibody can provide effective protection[19].

VACCINE EFFICACY

The efficacy of vaccinating dams with fimbriae to protect suckling neonates against ETEC infection, via passive lacteal immunity, was first convincingly demonstrated by Rutter and Jones, using F4 fimbriae in swine[20]. Subsequent work confirmed the efficacy of the approach and generalized the concept by extending it to other ETEC fimbriae and other animal species[21–25]. It also demonstrated that ETEC fimbriae apparently do not have cross-protective epitopes and, therefore, vaccines are most useful if they contain the fimbrial antigens prevalent in the target host species[22]. Most of the vaccines in current use probably achieve this by including F5 in vaccines for cattle or by combining F4, F5 and F6 in those for pregnant swine.

Although F1 and F41 fimbriae are prevalent among animal ETEC, their efficacy as protective antigens in vaccines for cattle and swine is less well defined than is that for F4, F5 and F6[25–28]. Most animal ETEC which produce F1 or F41 also produce F4, F5 or F6. Vaccination of dams with F5 protects calves and pigs against ETEC strains bearing both F5 and F41 ($F5^+F41^+$)[28,29]. In a series of experiments utilizing a challenge strain (ETEC strain 431) which produces three fimbriae ($F1^+$, $F5^+$ and

$F41^+$), it was found that the strain produced F5 and F41, but not F1, in the small intestine of pigs during disease[22,29,30]. Vaccination with F5 protected against challenge with the strain, but vaccination with either F1 or F41 did not[22,29,30] However, vaccination with F41 did protect piglets against challenge with an $F5^-F41^+$ ETEC strain, and F41 vaccines are apparently more effective than F5 vaccines in protecting mice against $F5^+F41^+$ ETEC[29,31]. The controversy as to the role, if any, of F1 fimbriae in the pathogenesis of ETEC infections and their efficacy as protective antigens in vaccines to prevent the disease has been discussed[28,30,32,33].

There is convincing evidence that vaccination of pregnant swine with antigens directed against the heat labile enterotoxin (procholeragenoid or LT_B) protects piglets (born to and suckling the vaccinates) against challenge with LT^+ ETEC[34–36]. The principal barrier to more general development of antitoxic vaccines is the fact that many porcine ETEC strains produce one or both of the heat stable *E. coli* enterotoxins (STa and STb) in addition to or instead of LT. Most bovine ETEC produce STa only. In contrast to LT, neither STb nor STa are antigenic and both are rapidly excreted from the bacterial cell, rather than concentrated near the bacterial surface (periplasmic space) like LT. Furthermore, STa has not been an effective protective antigen when used as a hapten in vaccines which stimulated the production of STa neutralizing antitoxin[37,38]. Most porcine ETEC which produce LT also produce STb[39]. Vaccination with procholeragenoid or LT_B protects against such LT^+STb^+ ETEC[34,36]. The mechanism of such LT induced protection against the antigenically unrelated STb enterotoxin has not been defined. It could reside in the apparent antibacterial or anticolonizing effect of such LT vaccines[36].

Some vaccines include polysaccharide O (cell wall) and K (capsular) antigens representing some of those most common among porcine or bovine ETEC. There is conflicting evidence regarding the efficacy of O antigen based vaccines[1]. In one series of experiments, O antigens were not effective, but a true capsular polysaccharide K antigen of the A (mucoid, heat stable) variety did appear to be effective[40]. Regardless of their efficacy, the practical value of O or polysaccharide K antigens is limited by the multiplicity of O and K antigens that commonly occur among ETEC, i.e. vaccines of reasonably limited valency would not be expected to provide broad efficacy. Furthermore, many ETEC lack true polysaccharide (A variety) capsules.

The USDA licensure policy recognizes the proprietary nature of efficacy data on specific commercial products. Publication of efficacy data related to vaccines licensed in the US is not required. Field trials indicating efficacy of a fimbriae based vaccine in swine, and lack of efficacy of a combined F5, rotavirus, and coronavirus vaccine in dairy cattle, have been published[25,41]. Field trial data demonstrating the efficacy of most of the products in commercial use in the US are not available. The USDA does receive and investigate consumer reports concerning the safety or efficacy of licensed vaccines in commercial use. A total of 32 such reports were received by the USDA, Animal and Plant Health Inspection Service, Veterinary Biologics Field Operations, for all products of the type listed in *Table 1* during the period from October 1983 to January 1992. Five of the 32 reports concerned efficacy. We assume that most complaints are directed to the manufacturers rather than to the USDA, and that the total number of complaints received is much higher than those reported to the USDA. Nevertheless, the low number of reports received by the USDA during more than eight years of use is consistent with the anecdotal reports, as well as the prevailing opinion of animal health professionals and livestock producers, that the vaccines are effective in commercial use.

Data to indicate if the incidence of morbidity or mortality due to ETEC infections has changed since the introduction of commercial vaccines are not available. The national survey of US swine health found that 15% (1.5 pigs/litter) of the piglets born alive during the period from December 1989 to January 1991 died before they reached one month of age[18]. Diarrhoea was reported as the most common illness observed, and nearly 11% of all deaths during the first month after birth were attributed to diarrhoea (*Table 2*). Forty-seven per cent of the producers in the survey reported routine vaccination of dams to prevent ETEC infection of the piglets (*Table 3*). It was not determined if the percentage of illnesses or deaths attributed to diarrhoea in herds reporting routine vaccination was different from that in

Table 2 National Swine Survey[a]: piglets (≤one month old)

	Percentage of total	
Illness/condition	Cases	Deaths
Diarrhoea	58	11
Crushed	–	44
Starvation	–	19
Deformities	2	1
Lameness	3	1
Respiratory	2	1
Other	35	23

[a]NAHMS; USDA, APHIS, 1991, included 712 farms and 313576 piglets[18]

Table 3 National Swine Survey[a]: routine vaccination reported

	Percentage of farms	
Agent/disease	Dams	Piglets[b]
Leptospirosis	70	–
Parvovirus	65	–
Erysipelas	61	47
Escherichia coli	47	12
Atrophic rhinitis	38	42
Transmissible gastroenteritis[c]	24	4
Clostridium perfringens	22	8
Pseudorabies	22	2
Rotavirus	16	–

[a]NAHMS; USDA, APHIS; 1991[18]
[b]Includes both vaccines and antiserum
[c]Coronavirus

Table 4 National Swine Survey[a]: number of piglet illnesses and deaths attributed to diarrhoea

	Age in weeks				
Event	1	2	3	4	4+
Illness	9805	3475	1161	303	119
Death	2265	929	287	101	41

[a]NAHMS; USDA, APHIS; 1991[18]

Table 5 Agents associated with piglet and calf diarrhoea, 1991[a]

Agent	Piglets		Calves	
	Number examined[b]	Percentage positive	Number examined	Percentage positive
Enterotoxigenic *E. coli*	630	23	2096	26
Coccidia	370	16	1389	5
Rotavirus	589	11	2463	24
Coronavirus	609	8	2236	20
Clostridium perfringens	340	3	75	15
Cryptosporidia	–	–	2054	28
Salmonella	–	–	2925	9

[a]NAHMS; USDA, APHIS; *DxMonitor*[42]
[b]15 laboratories – 6 months

herds that did not. The survey did not report the causes of diarrhoea in the herds surveyed. However, most of the illnesses and deaths attributed to diarrhoea occurred during the first week after birth (*Table 4*), which is the period when most fatal ETEC infections occur. Furthermore, the combined results from several veterinary diagnostic laboratories in the US indicate that ETEC were a common cause of piglet diarrhoea during 1991 (*Table 5*)[42].

National survey data on cattle health in the US are not yet available. However, results from veterinary diagnostic laboratories also indicate that ETEC infections were a common cause of calf diarrhoea in the US during 1991 (*Table 5*)[42]. Thus ETEC infections continue to be a significant clinical problem among calves and piglets in the US in spite of extensive vaccination. The proportion of the problem that occurs in the offspring of properly vaccinated dams is not known. The prevailing perception among animal health professionals is that the vaccines are effective in the field and that the disease occurs principally among non-vaccinated or inadequately vaccinated animals. Some veterinarians also have the perception that in some swine herds vaccination moves the peak prevalence of clinical disease from the first to the second or third week after birth, thereby significantly reducing mortality but not morbidity (J. McKean, personal communication).

It should be possible to extend passive protection beyond the first week into the later suckling period, through the use of oral vaccines or by using combined oral and parenteral vaccination[43].

ANTIGEN DRIFT

It is rational to hypothesize that extensive use of fimbrial based vaccines will select against the prevailing fimbrial antigen types as reflected in the vaccines and for the emergence of new or previously low prevalence fimbrial antigens. Fimbriae antigenically distinct from F1, F4, F5, F6 and F41 occur among animal ETEC[28,44]. These other antigen types are apparently less prevalent than those currently used in commercial vaccines. The role of these other fimbriae in pathogenesis is less well defined than that of F4, F5 and F6. F^- variants of $F4^+$ and $F5^+$ ETEC frequently emerge during the course of ETEC infections in animals, apparently as the result of selection pressure exerted by antibody against F4 or F5 fimbriae[45–48]. It has been suggested that extensive F4 vaccination may have caused the emergence of $F5^+$ ETEC and the ad variant of F4 among swine in Europe[49,50]. An argument against the hypothesis of vaccine induced selection pressure as the reason for the emergence of $F5^+$ and $F4ad^+$ ETEC in European swine has been presented[28].

Wilson and Francis found that 91% of 223 ETEC collected from US piglets between 1980 and 1982 were accounted for by F4 (48%), F5 (13%) and F6 (30%)[27].This is probably an accurate reflection of the prevalence of these three fimbrial antigens among porcine ETEC in the US prior to extensive use of the commercial vaccines. These three fimbrial antigens continue to be commonly associated with ETEC infections among US piglets. For example, the Department of Veterinary Diagnostic Investigation at the University of Minnesota diagnosed 918 swine accessions (one or several pigs examined/accession) as ETEC infection during a period from 1988 to 1991[51–53]. They reported 1108 positive immuno-fluorescence tests for these three fimbrial antigens among those accessions. Eighty-five per cent of the positive tests were F4, 6% were F5 and 9% were F6.

The ratio of F4/F5 plus F6 in the Wilson and Francis report is 1.1/1, compared to 5.7/1 in the Minnesota reports. We speculate that this apparent shift to $F4^+$ ETEC is somehow a reflection of vaccination. It suggests that since the advent of vaccination, $F5^+$ and $F6^+$ ETEC infections are controlled more effectively than those due to $F4^+$ ETEC. It may reflect a shift of peak disease prevalence from the first to the second, third and fourth weeks after birth. $F4^+$ ETEC cause disease through that age span, while $F5^+$ and $F6^+$ ETEC infections are confined principally to the first few days of age, when vaccine induced milk (colostral) antibody titres are highest and vaccines would be expected to be most effective. This age shift would be consistent with the perception of some US veterinarians cited earlier and with the effects of extensive use of $F4^+$ vaccines in Europe, reported by Söderlind *et al.*, a decade ago[50]. There are no data to indicate whether the apparent shift in prevalence is due to a decreased incidence of disease during the first week after birth, to an increased incidence of disease during the second and later weeks, or both.

The high prevalence of $F4^+$ ETEC infections could also reflect the emergence of antigenic variants of F4 as was suggested to occur in Europe[49]. We are not aware of recent data on the prevalence of porcine ETEC which do not produce F4, F5, F6 or F41 ($4F^-$ ETEC). We would expect vaccine induced selection pressure to increase the prevalence of $4F^-$ ETEC above the 8% reported by Wilson and Francis[27].

POSTWEANING ETEC INFECTIONS

Most ETEC vaccine development in animals has focused on the problem that occurs during the early neonatal period (first week after birth). However, in swine a high incidence of ETEC infection also occurs immediately after weaning. In the US, piglets are usually weaned at 3–4 weeks of age. The trend is toward weaning at <3 weeks of age. Mortality rates among affected pigs are lower for the postweaning disease than for the neonatal disease. The pathogenesis of the postweaning disease is similar to the neonatal disease in that fimbriae and enterotoxin are required virulence attributes of the associated ETEC. However, the postweaning disease appears to be more complex in that multiple factors predispose to, or cause, clinical disease. Some of these apparent predisposing causes are social and physical stress, diet, increased gastric pH, concurrent rotavirus infection, and cessation of the local protection provided by the antibody ingested with milk at each suckling. Cost-effective control of the disease centres around hygiene and management to minimize predisposing causes. Antimicrobial drugs are commonly used prophylactically and therapeutically.

It is logical to extend the concept of fimbrial vaccines to include postweaning ETEC infections. Commercial vaccines prepared as killed $F4^+$ strains of ETEC isolated from the postweaning disease are available in the US. One of the products is designed for parenteral administration to piglets prior to weaning and the other is designed to be fed for several weeks during the suckling and immediate postweaning periods. Data to support the rationale and efficacy of such vaccines are limited[54–57]. Parenteral vaccines tend to stimulate the systemic rather than the mucosal immune system. Inadequate delivery of systemically produced IgG from blood to the intestinal lumen limits the efficacy of parental vaccines for ETEC because these agents remain in the lumen of the intestine, on the epithelial surface. Oral vaccines stimulate the mucosal immune system to produce secretory antibodies that are efficiently transported into the intestinal lumen. Live ETEC are effective oral fimbrial vaccines but killed ETEC have generally been less effective[43,55–59]. Recent efforts have focused on development of live oral fimbrial based vaccines to prevent postweaning ETEC infections in swine[60–62]. Such a vaccine would ideally:

- temporarily colonize the small intestine of the suckling pig in spite of the antifimbrial antibody ingested with milk
- not produce enterotoxin or other substances that would adversely affect the health and productivity of the colonized piglet
- stimulate the mucosal immune system of the <3-week-old pig to secrete protective levels of antifimbrial IgA into the small intestine
- reflect the fimbrial antigens prevalent among ETEC associated with postweaning diarrhoea.

The fimbrial antigens of ETEC associated with postweaning diarrhoea of swine differ somewhat from those associated with the disease in neonates[63–67]. Most pigs are physiologically resistant to colonization by $F5^+$ or $F6^+$ ETEC by about a week of age[68–71]. Thus, these strains are not commonly associated with the postweaning disease[26,65]. Age resistance to $F5^+$ ETEC appears to be due, at least in part, to decreased availability (with age) of receptors for F5 on epithelial cells[68]. On the other hand, resistance to F6 correlates with an increased availability of receptors in mucus[69]. Receptors in mucus apparently prevent contact of $F6^+$ ETEC with receptors on the epithelial surface[70]. Receptivity of swine intestinal mucus for F4 also increases with age[72]. However, this increase is not adequate to protect genetically susceptible pigs from colonization, and $F4^+$ ETEC are associated with disease in both the neonatal and postweaning periods. The fimbrial antigens (other than F4) associated with postweaning ETEC infections have not been well defined. It seems likely that additional, as yet unrecognized, fimbrial antigen types are prevalent at this age[73,74]. There is suggestive evidence that during the first three weeks after birth, swine intestine becomes progressively more receptive to adhesion and colonization by ETEC of these unrecognized fimbrial antigen types[75].

HOST RESISTANCE AND RECEPTOR AVAILABILITY

The pattern emerging is that variations in the availability of receptors for fimbriae affect ETEC infections in several different ways. Inheritance of the trait for expression of F4 fimbrial receptors on intestinal epithelial cells is an autosomal dominant character[76,77]. Swine of the homozygous recessive genotype lack the required specific F4 receptors and are resistant to $F4^+$ ETEC both as neonates and during the postweaning period[78,79]. Variations in F4 receptor phenotype exist and correlate with antigenic variations among F4 fimbriae[80]. It has been suggested that selection pressure exerted by variation in receptor availability may be an alternative to that exerted by antibody, in the evolution of antigenic variants of F4 fimbriae[81]. Genetic control of receptor expression may also influence resistance to *E. coli* of other as yet unrecognized fimbrial antigen types associated with postweaning disease in swine[82–84].

On the other hand, changes with age in the availability and distribution of receptors apparently determines susceptibility and resistance to some ETEC. For example, the availability on epithelial cells of receptors for F5 decreases with age, while the availability of those for some postweaning ETEC increases[68,75]. The availability in intestinal mucus of receptors for F4 and F6 fimbriae increases with age[69,72]. Older pigs that are genetically susceptible to F4 (have F4 receptors on intestinal epithelial cells) remain susceptible to F4 through the postweaning period in spite of the receptivity of intestinal mucus[72,79]. However, the receptivity of the mucus in older pigs for F6 is apparently great enough to prevent interaction between F6 and receptors on intestinal epithelial cells[69,70], apparently protecting older pigs against $F6^+$ ETEC by preventing intensive colonization of the small intestine.

These examples suggest that strategies to control the availability of receptors for fimbriae may provide alternatives to vaccination in the control of ETEC infections[77,85].

CONCLUSIONS

Federally licensed vaccines to prevent ETEC infections in neonatal calves and pigs have been used extensively in the US for about a decade. Most of the vaccines are based on the prevailing fimbrial antigens required for colonization by ETEC in calves (F5) and newborn pigs

(F4, F5 and F6). The vaccines are given to pregnant females to produce antifimbrial antibody in colostrum and milk. Such lacteal antibodies will passively protect the intestine of the suckling neonate against colonization by ETEC during the highly susceptible early neonatal period. Data on the efficacy of the commercial vaccines during the decade of routine use are not available. They continue to be generally regarded as effective. However, ETEC infections continue to be a common problem among neonatal calves and pigs in the US. Data to indicate whether the problem occurs principally among animals suckling vaccinated or non-vaccinated dams are not available. There are unpublished anecdotal reports that in some swine herds vaccination has moved the peak incidence of morbidity from the first to the second or third week after birth. The high ratio of $F4^+$, as compared to $F5^+$ and $F6^+$, ETEC infections, among swine submitted to a diagnostic laboratory, is consistent with such anecdotal reports, because piglets are physiologically susceptible to F5 and F6 ETEC only during the first week after birth.

There is no evidence that ETEC with novel colonization mechanisms or new fimbrial antigens have emerged under the selection pressure of vaccination. Nor is there evidence that previously 'low prevalence' fimbrial antigen type ETEC, not represented in the vaccines, have emerged as 'common pathogens' filling an ecological niche left by the fimbrial antigen types targeted by the vaccines. Admittedly there is apparently no active direct surveillance for such events, and such events could explain the continued common occurrence of neonatal ETEC infections among swine in the face of intensive vaccination. It seems unlikely, however, that such events could account for a high incidence of disease and go unrecognized, because fimbrial antigen testing for F4, F5 and F6 is routinely used in the laboratory confirmation of ETEC infections. A high incidence of disease caused by $3F^-$ ETEC would be likely to be recognized and reported.

The knowledge and technology for the general development of fimbrial vaccines to control postweaning ETEC infections in swine is not yet available. The fimbrial antigens of the ETEC prevalent at this age have not been well defined. Immunological approaches to establishing and maintaining protective levels of antifimbrial antibody in the small intestine of the pig during the first 1–2 weeks after weaning have not been developed.

From the comparative medical perspective, the experimental studies in farm animals demonstrate that fimbrial vaccines can protect against ETEC infections. Practical or cost-effective use in animals has been possible because animals are most susceptible to the disease during the first few days after birth, when the intestine of the suckling animal can be protected with colostrum and milk antibody produced by vaccinating the dam. Strategies for general (commercial) extension of the concept beyond passive lacteal immunity for the early neonatal period in animals have not yet been developed. The task of extending the concept to humans, where protection is needed not only during the nursing period but also after weaning and throughout childhood, is clearly a much greater, but rational, challenge.

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