Punti chiave per il controllo delle colibacillosi

Keys for controlling colibacillosis with restricted use of antimicrobials

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Digestive and Respiratory Range
Swine Business Unit

SOCIETÀ ITALIANA DI PATOLOGIA ED ALLEVAMENTO DEI SUINI

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Outline

1. Understanding *E.Coli*

- *E.coli* characterization
- Why *E.coli* is the king of antimicrobial resistance?
- Clinical signs and pathogenicity of ETEC and VTEC
- Risk factors

2. Management of Edema disease

- Strategies against ETEC and VTEC
- Solutions
  - Diagnostic
  - Nutrition
  - Management
  - Immunity

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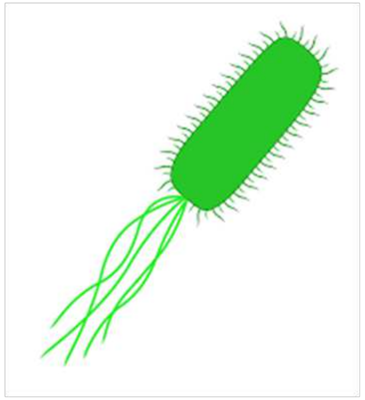
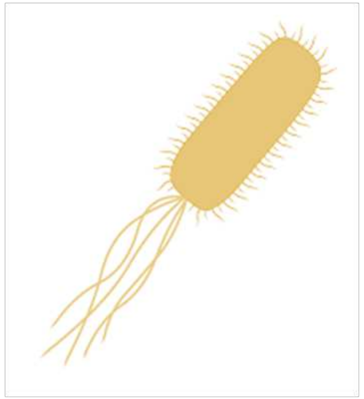
E.coli sp. characterization

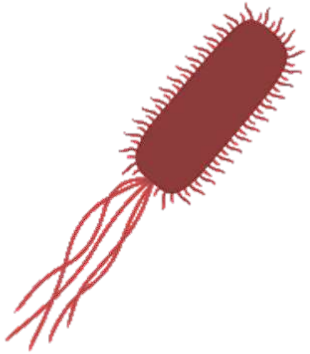
Gram-negative facultatively anaerobic rod (family *Enterobacteriaceae*)



Commensal



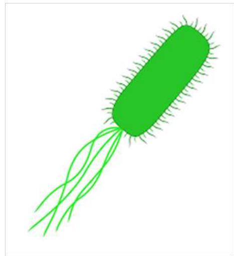
Potentially pathogenic



Pathogenic

Sampling

Intestinal/extra-intestinal tissue samples, feces, or rectal swabs



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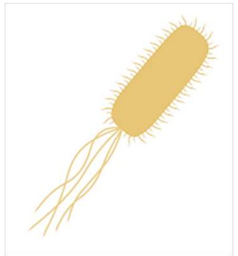

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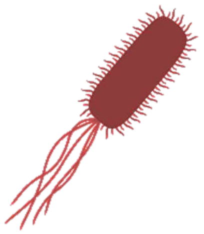


Pathogenic

E.coli sp. field characterization

Gram-negative facultatively anaerobic rod (family *Enterobacteriaceae*)

MALDI-TOF (spectrometry) → Common fast and cheap method. No pathogenic

Bacterial growth (traditional microbiology) – haemolytic?

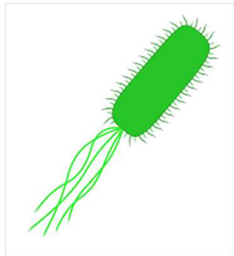
Bacterial growth →**PCR**
→**Identification of virulence factors (PCR): <u>Pathotypes</u>**

} more information

Picking colonies = excluding others!

Direct PCR → Identification of virulence factors (PCR): <u>Pathotypes</u> → Common fast method

E.coli sp. characterization



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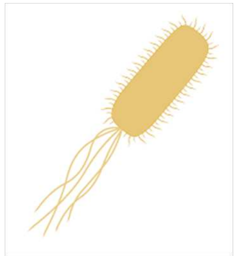
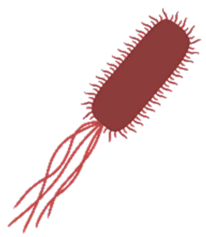


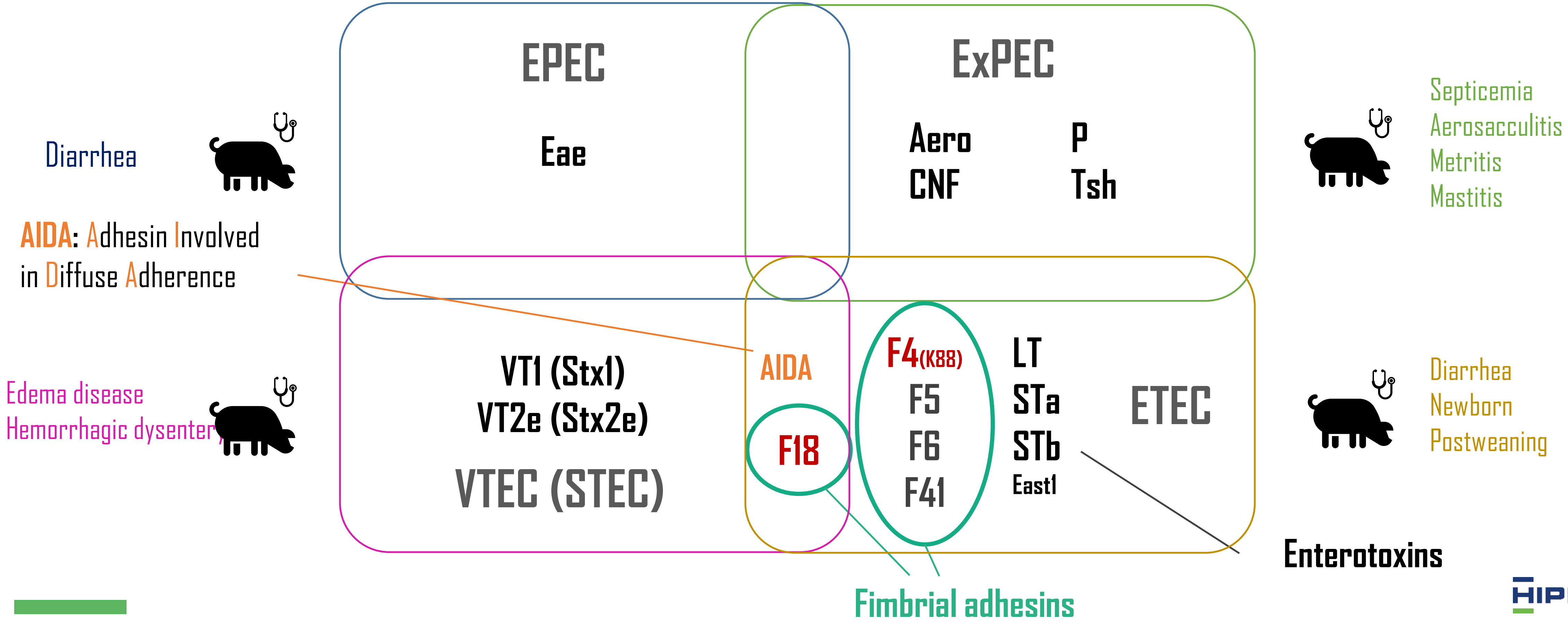
Potentially pathogenic



Pathogenic

Classification by pathotypes

Based on virulence mechanisms (presence of a particular virulent factor)



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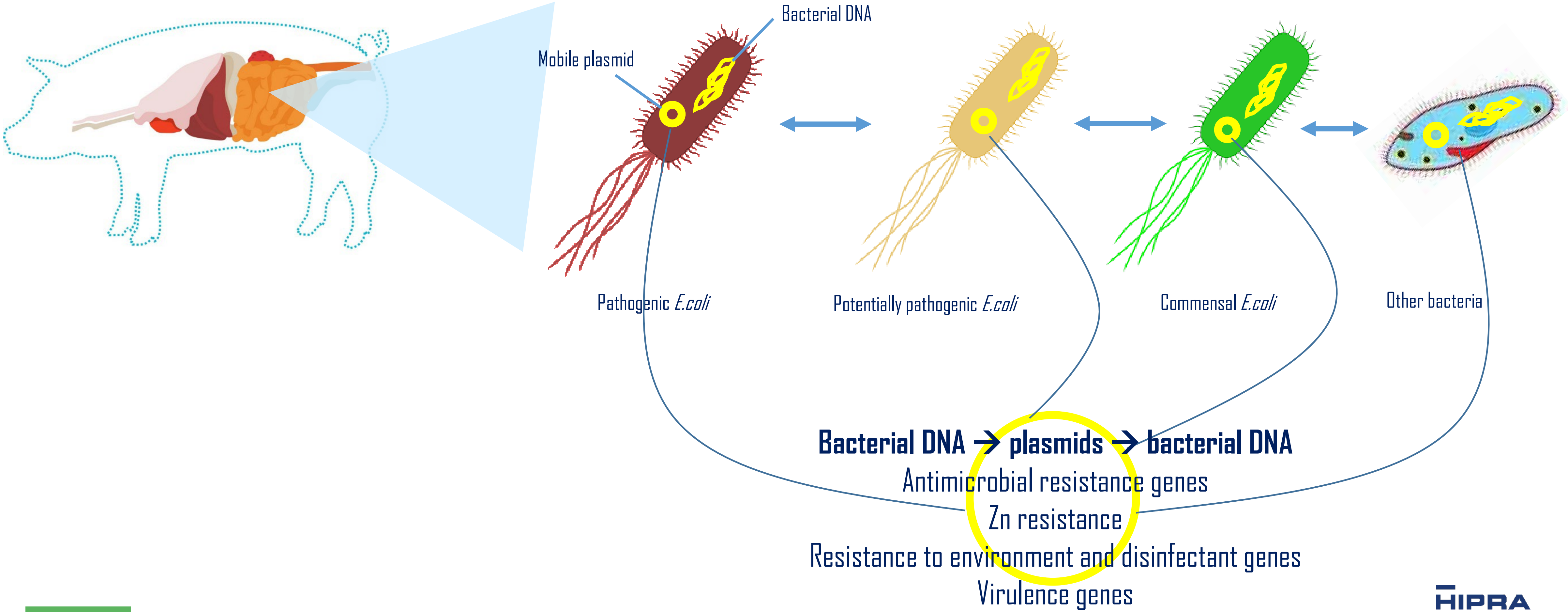
Why *E.coli* sp is the king of antimicrobial resistance?



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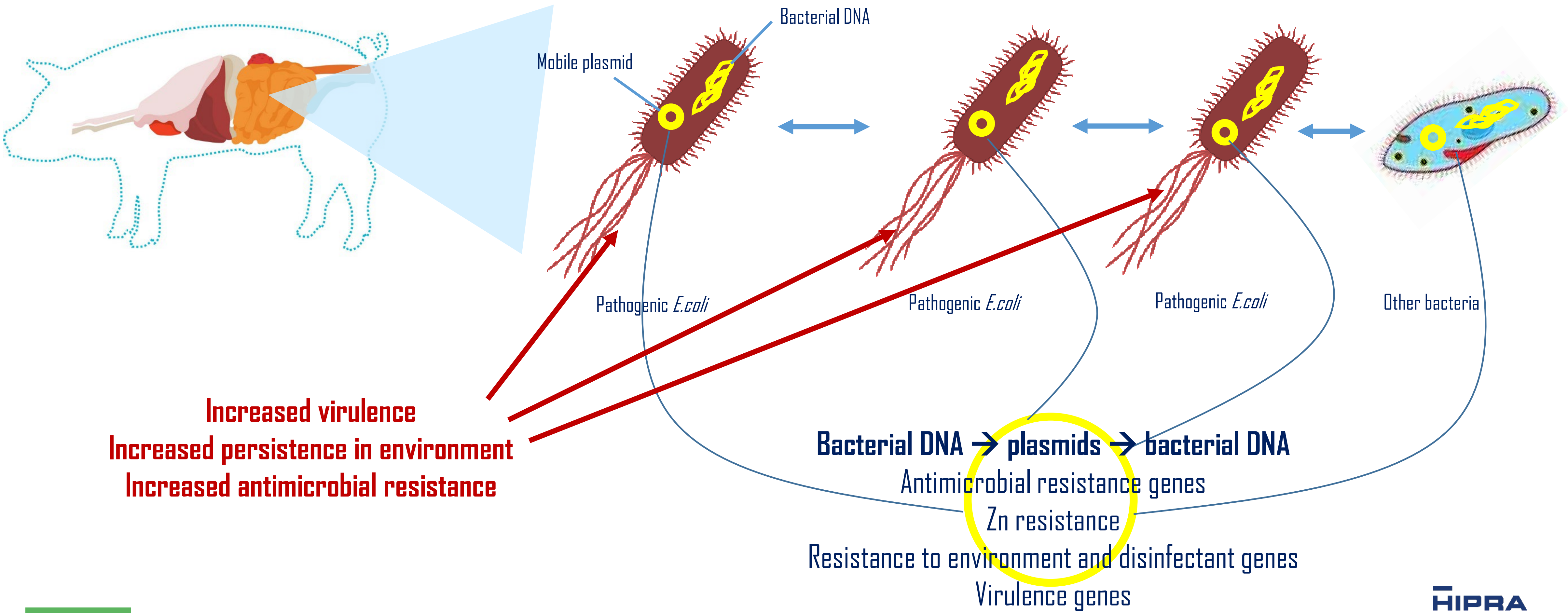

Why *E. coli* is the king of antimicrobial resistance?

frontiers in Microbiology

ORIGINAL RESEARCH
published: 05 November 2018
doi: 10.3389/fmicb.2018.02659

Swine Enteric Colibacillosis in Spain: Pathogenic Potential of *mcr-1* ST10 and ST131 *E. coli* Isolates

Epidemiological study of **499** *E. coli* **isolates** recovered **outbreaks of enteric colibacillosis (diarrhea)** in Spain

Antimicrobial resistance of the isolates

Antimicrobial agent	No. of resistant isolates (%)[a]
Colistin	65 (100)
Ampicillin	49 (75.4)
Ticarcillin	48 (73.8)
Ampicillin-sulbactam	42 (64.6)
Aztreonam	5 (7.7)
Ceftazidime	1 (1.5)
Cefepime	6 (9.2)
Cefotaxime	7 (10.8)
Gentamicin	31 (47.7)
Tobramycin	31 (47.7)
Minocycline	27 (41.5)
Fosfomycin	3 (4.6)[b]
Chloramphenicol	38 (58.5)
Trimethoprim-sulfamethoxazole	47 (72.3)
Nalidixic acid	39 (60.0)
Ciprofloxacin	8 (12.3)
Levofloxacin	7 (10.8)

[a]Isolates showing intermediate resistance were considered as resistant. None of the 65 mcr-1-positive E. coli isolates showed resistance to piperacillin-tazobactam, imipenem, meropenem, amikacin, or tigecycline. [b]Additionally, eight isolates showed a MIC value = 64. According to EUCAST, the cut-off point is 32 mg/L and higher values are considered resistant, while for CLSI it is 64.

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  - Vaccination

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Pathogenicity ETEC and VTEC

- Worldwide problem, may be endemic or occur as outbreaks

- First weeks after weaning >introduction at fattening units (rare)

ETEC: Post Weaning Diarrhea (PWD)

- Presentation:
  - **Mild**: aprox. 2% mortality + lower weight gain
  - **Severe:** aprox. 25% mortality + sudden death

VTEC: Edema Disease (ED)

- Presentation:
  - **Clinical**
    - Sudden death
    - Eyelid edema, incoordination, respiratory distress, recumbency and death
    - Mild subcutaneous edema, pruritus and recovery
  - **Chronic**
    - Decrease growth rate, nervous signs, muscle atrophy
  - **Subclinical**
    - Decrease growth rate

Pathogenicity ETEC

1. Ingestion of ETEC

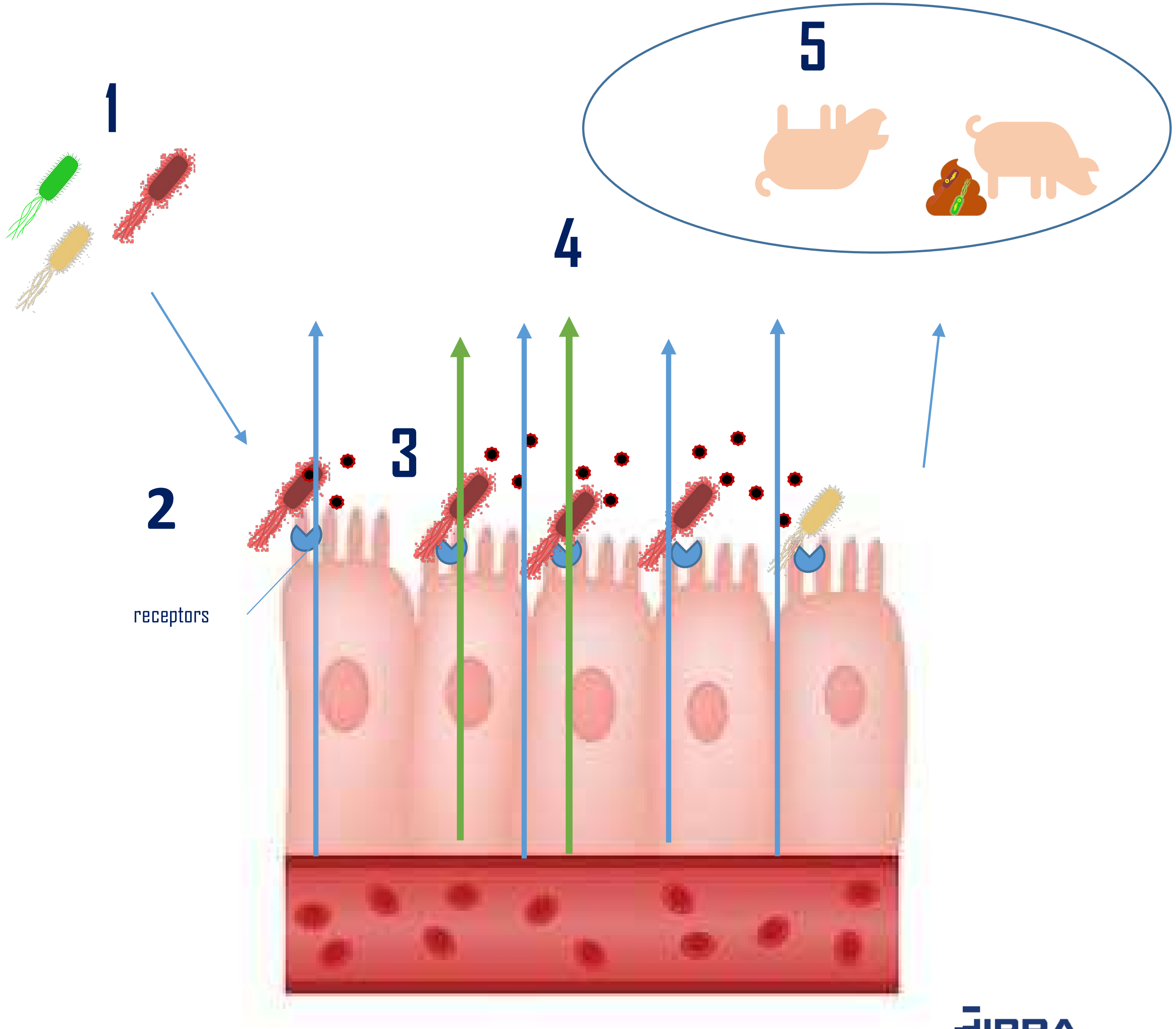
2. Colonization small intestine (receptors in jejunum & ileum)

- **ETEC:F4** - present from birth
  - cause diarrhea rapidly (after 1-2 days)
  - peak excretion after 3-5 days
  - neonatal and PWD
- **ETEC:F18** - age dependant (+10 days?/+20 days?) → 3 weeks ↑
  - cause diarrhea slowly (after 5-7 days)
  - late-lactation and PWD
- **AIDA**

3. Production of enterotoxins

4. Water and electrolyte loss

5. Diarrhea, weight loss and death



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Pathogenicity VTEC (STEC)

1. Ingestion of VTEC

2. Colonization small intestine (receptors in jejunum & ileum)

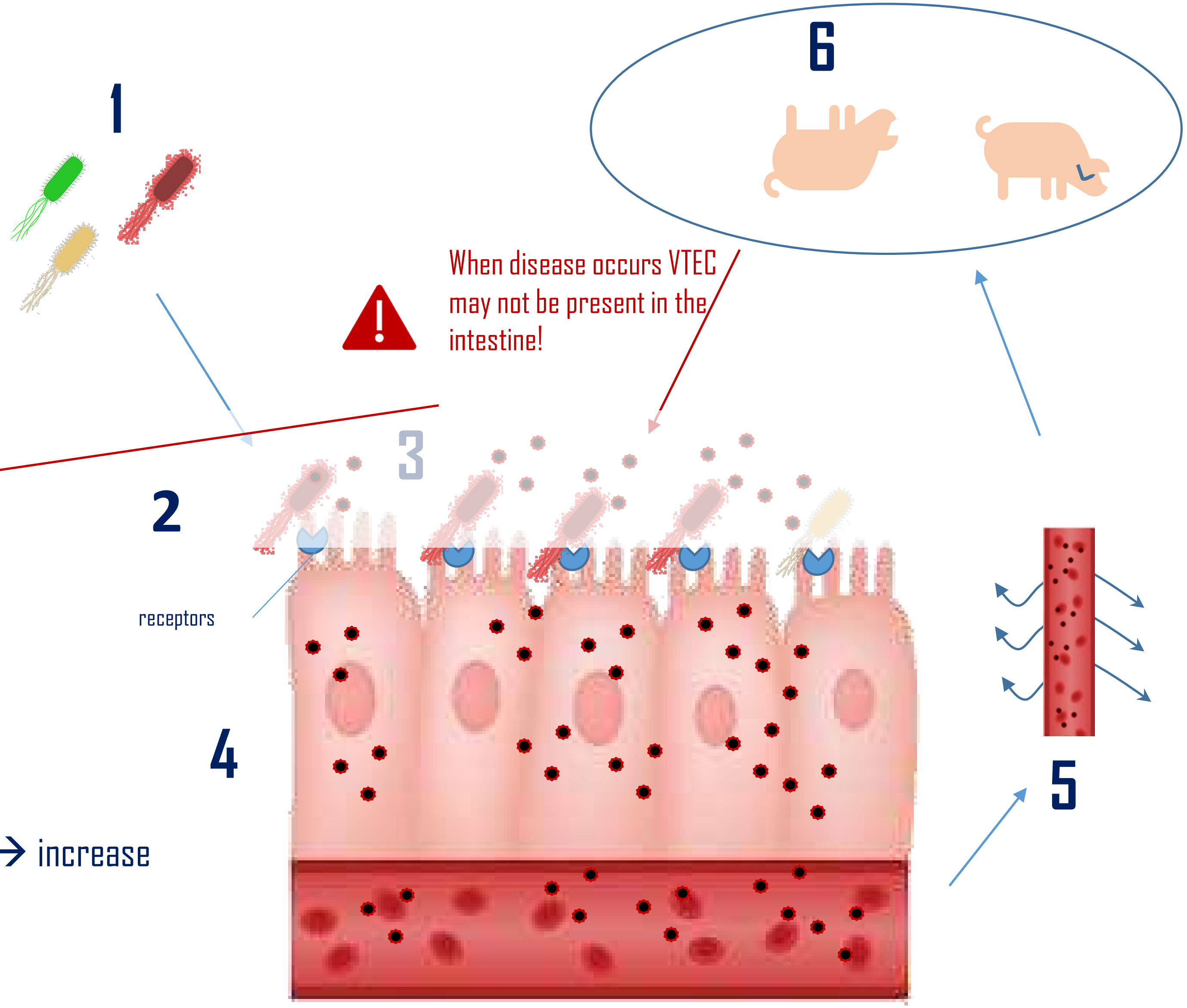
- ~~ETEC:F4~~
- **ETEC:F18** - age dependant (+10 days?/+20 days?) → 3 weeks ↑
  - cause disase slowly (after 5-7 days)
  - late-lactation and PWD
- **AIDA?**

3. Production of verotoxins (Vt2e/Stx2e)

4. Transport of toxins to circulation

5. Affection blood vessels: degenerative angiopathy small arteries → increase vascular permeability + epithelial necrosis

6. Edema, ataxia and death



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Pathogenicity ETEC and VTEC (STEC)

Mixed infections are common

- ETEC + VTEC (or ETEC and VTEC in one bacteria)
- ETEC + other pathogens *(Clostridium, Salmonella, Lawsonia, Brachyspira,…)*

frontiers in Microbiology
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Epidemiological study of **499 *E. coli* isolates** recovered **outbreaks of enteric colibacillosis with diarrhea** in Spain

	Samples	%
ETEC	277	57,5 %
aEPEC	156	32,4 %
STEC/ETEC	33	6,8 %
STEC	15	3,2 %

Increased pathogenicity

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Risk factors Edema Disease and PWD

	Etiology	Risk factors	
Disease	*E. coli* pathotype	Host	Environment
Edema disease	STEC:F18 STEC: AIDA?		
Post-weaning diarrhea	ETEC:F4, F18, ETEC:AIDA, EPEC, mixed *E. coli* pathotypes		

Adapted from Diseases of Swine 11th Ed.

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Risk factors Edema Disease and PWD

ZnO ban in 2022

Need for alternatives to control enteric disorders
(mainly colibacilosis)

Table 1- Zinc oxide: 2 different uses - 2 different situations.

	ZnO as a feed additive	**ZnO as a veterinary medicinal product (VMP)**
EU agency	European Food Safety Authority (EFSA)	European Medicines Agency (EMA)
Legislation	Regulation (EC) No 1831/2003 on additives for use in animal nutrition	Directive 2001/82/EC on veterinary medicinal products + Regulation (EC) No 726/2004
Levels	Max. total 150ppm of zinc (from ZnO and other sources)	Normal dosage ca. 2500ppm
Ban?	No! There is no indication that ZnO will be banned as a feed additive.	Yes! Marketing authorisations for ZnO-based VMPs will be withdrawn the across EU by June 2022.

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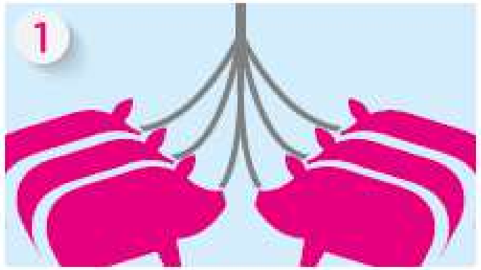
Strategies against ETEC and VTEC

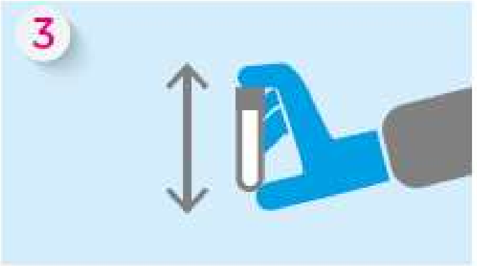
Diagnostic

VERO CHECK by VEPURED®

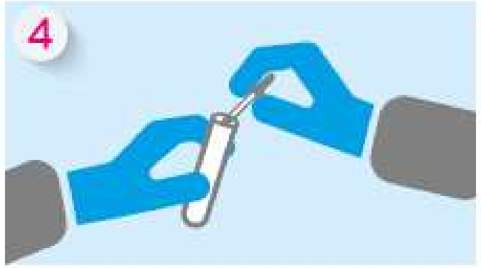


Oral fluid collection.

Enter all the information requested in the leaflet.



Oral fluid should be shaken 3 times before FTA Card inoculation.



Submerge the pipette press on the lower stop until the pipette tube is completely full (100 µl).

Dispense the entire contents of the pipette on to the circle.

The FTA card must be allowed to dry for at least one hour at room temperature.

Insert the FTA card into the plastic bag and the desiccant bag. Place it inside the HIPRA envelope with this leaflet.

Diagnostic results will be available via HIPRALink® DIAGNOS App or webpage.

The circle must be inoculated twice, so steps 3, 4 and 5 have to be repeated once more.

Strategies against ETEC and VTEC

Reduce number of pathogenic *E. coli*

Increase resistance of animals to infection

Nutrition

Management Facilities

Immunity

Strategies against ETEC and VTEC

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Nutrition against ETEC and VTEC

Reduce number of pathogenic *E. coli* and increase resistance of animals

Water

- Additives: Organic and inorganic acids

Ingredients (diet)

- Highly digestible
- Milk-based protein
- Reduced protein (<18%)
- Restricted feed intake
- Increase fibre
- Mash vs pelleted feed
- Reduce calcium levels 10% (buffer capacity)

Feed supplements

- Organic and inorganic acids
- Essential oils
- ZnO
- Antimicrobial peptides
- Spray-dried plasma
- Beta-glucans
- Probiotics
- Prebiotics
- Oligosaccharides: FOS, GOS, MOS
- Enzymes

Nutrition against ETEC and VTEC

Reduction of protein (<18% or <180g/kg)

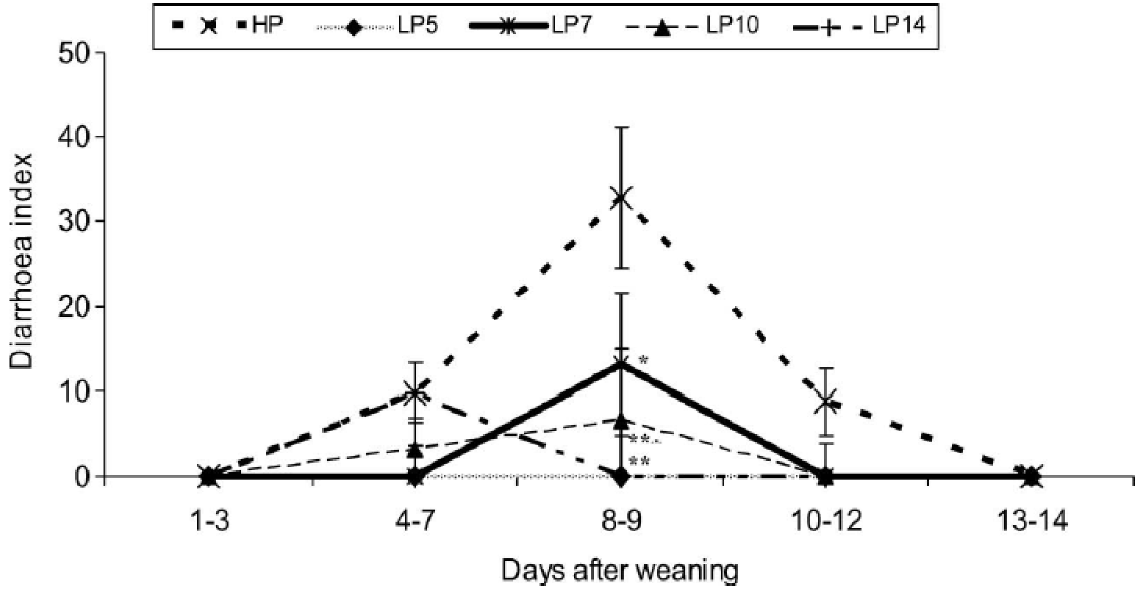
HP = high protein (24,3%)
LP5 = low protein (17,3%) fed for 5 d after weaning
LP7 = low protein (17,3%) fed for 7 d after weaning
LP10 = low protein (17,3%) fed for 10 d after weaning
LP14 = low protein (17,3%) fed for 14 d after weaning

Effect

- Reduce proteolytic bacteria

How?

- Use high valuable proteins: plasma, lactic proteins
- Complement with synthetic aminoacids to achieve ideal Aa's profile



Heo et al. 2008

Diets under 18% protein at weaning may fail to achieve maximal pig performance (even when supplemented with synthetic Aa's)

Nyachoti et al. 2006

Nutrition against ETEC and VTEC

Probiotics

Live micro-organisms which when administered in **adequate amounts** confer a **health benefit** on the host (FAO/WHO 2001)

Enormous research to reduce ETEC, VTEC and other pathogens

Benefits?

Barba-Vidal et al. 2018

Table 1 *Pig in vivo scientific works evaluating the use of probiotics against digestive bacterial pathogens (Escherichia coli and Salmonella sp.)*

	Probiotic	Pathogen	Animals		
References	Strain, dose per pig and dosing method	Strain and dose per pig	Days old: weaning → Inoculation	Benefits	Main results
De Cupere *et al.* (1992)	(a) *Bacillus cereus var. Toyoi* (1×10^9 cfu/g) (b) *Lactobacillus* spp. (7.5×10^7 cfu/g) (c) *Streptococcus faecium* (5.6×10^8 cfu/g) Included in feed	*Escherichia coli* 0141 K85 (10^9 cfu)	28 → 30	No	No improvements on clinical symptoms or mortality. No improvements on fecal *E. coli* shedding
Shu *et al.* (2001)	*Bifidobacterium lactis* HN019 (10^9 cfu/day) Oral administration	*E. coli* sp.	21 → natural acquisition	Yes	Reduced diarrhea scores and fecal shedding of *E. coli*. Improved animal performance. Increased T-cell differentiation and pathogen-specific antibody titers
Bhandari *et al.* (2008)	*Bacillus subtilis* (6×10^8 cfu/kg) Included in feed	*E. coli* K88 (4×10^{10} cfu)	17 → 24	Yes	Reduced diarrhea scores and mortality. Modulated microbial diversity.
Lessard *et al.* (2009)	(a) *Pediococcus acidilactici* (b) *Saccharomyces cerevisiae* (c) *P. acidilactici* + *S. cerevisiae* Lactation (10^9 cfu). Oral administration Weaning (10^9 cfu/kg). Included in feed	*E. coli* O149: F4 K88 (10^9 cfu)	21 → 49 + 50 + 51	Yes	Before challenge: (a) increased T-cell differentiation. After challenge: (a, b, c) Reduced bacterial translocation. (b) Increased ileal immunoglobulins
Zhang *et al.* (2010)	*Lactobacillus rhamnosus* GG (10^{11} cfu/day) Oral administration	ETEC 149: K91, K88ac (10^{10} cfu)	18 → 26	Yes	Reduced diarrhea scores and fecal coliform shedding. Modulated microbial diversity. Increased jejunal immunoglobulins. Modulated systemic inflammatory cytokines
Bhandari *et al.* (2010)	*E. coli* (4.5×10^{12} cfu) Included in feed (daily mix)[1]	*E. coli* K88 (1.2×10^{11} cfu)	21 → 27	Yes	Reduced ETEC in ileum. Improved animal performance
Wang *et al.* (2009)	*Lactobacillus fermentum* I5007 (2×10^9 cfu) Oral administration	*E. coli* K88ac (2×10^9 cfu)	21 → 21	Yes	Increased T-cell differentiation and ileum cytokine expression
Konstantinov *et al.* (2008)	*Lactobacillus sobrius* DSM 16698 (10^{10} cfu) Included in feed (daily mix)[1]	ETEC K88 O149 F4 (1.5×10^{10} cfu)	21 → 28	Yes	Reduced levels of ETEC in the ileum, improved performance and increased diarrhea
Krause *et al.* (2010)	*E. coli* (1.5×10^{11} cfu) Included in feed (daily mix)[1]	*E. coli* K88 (1.4×10^{10} cfu)	17 → 24	Yes	Increased animal performance and microbial diversity. Reduced diarrhea scores (in presence of raw potato starch)
Daudelin *et al.* (2011)	(a) *Pediococcus acidilactici* MA18/5 M (b) *S. cerevisiae* SB-CNCM I-1079 (c) *P. acidilactici* + *S. cerevisiae* Sows: gestation (3×10^8 cfu) + lactation (6×10^9 cfu). Included in feed (daily mix)[1] Piglets: lactation (1×10^9 cfu). Oral administration Weaning: 2×10^9 cfu/kg. Included in feed	ETEC O149 F4 (5×10^9 cfu)	21 → 28	Yes	(a, b) Reduced ETEC attachment to intestinal mucosa. (a,c) Induced ileum cytokine expression
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Nutrition against ETEC and VTEC

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Barba-Vidal et al. 2018

Conclusions:

- **Effects**: higher number of articles describing beneficial effects with of probiotics (>80%) rather than negative effects.
- **Against pathogens**:
  - majority of cases probiotic effects are positive, although they tended to be rather discrete.
  - potential risks: certain probiotics in animals with damaged gut health or pathogen pressure (translocation).
- **High variability**: probiotic strains that were not useful in one trial are useful in other ones. Differences in diets, dosing, genetics, management… may influence.

TAKE-AWAY

Probiotics may help BUT…

"Stop looking for probiotics as direct replacements for antibiotics.

Combine them with other feed, management or vaccination strategies"

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Strategies against ETEC and VTEC

Reduce number of pathogenic *E. coli*

Increase resistance of animals to infection

Nutrition

Management

Facilities

Immunity

Management against ETEC and VTEC

Reduce number of pathogenic *E. coli* and increase resistance of animals

Hygiene
- Cleaning, disinfection and drying
  - Pens
  - Feeders and drinkers
  - Other: farmer boots? Toys?
- Empty time (+4 days)
- Farrowing stage (less contaminated animals)

Facilities and environment
- Gate and floor design (avoid draughts, dry zone…)
- Temperature
- Humidity
- Feeder and drinker space

Management
- All-in/all-out
- Increase weaning age
- Transport
- Group sizes
- Densities
- Stress
- Sanitary control

Water
- Quality control

Management against ETEC and VTEC

Temperature

Low temperature

Chilling reduces intestinal peristaltic activity and consequently **increases bacterial colonization**

- Low temperatures in weaner → more PWD

Diseases of Swine. Fairbrother & Nadeau 2019.

TºC fluctuation

Higher **fluctuation increases** PWD occurrence

23.5±3°C	23.5±0,5°C
High PWD	Low PWD

Le Divich et al. 1994

Research | Open Access | Published: 18 June 2008

Risk factors for post-weaning diarrhoea on piglet producing farms in Finland

Taina M Laine, Tapani Lyytikäinen, Maija Yliaho & Marjukka Anttila

Acta Veterinaria Scandinavica **50**, Article number: 21 (2008) | Cite this article

Variable	P-value
Temperature control: Automatic vs. Manual	0.03
Number of sows	0.02
Only 1 feeder	0.08

Automatic temperature control in the accommodation of weaners reduced the risk of PWD

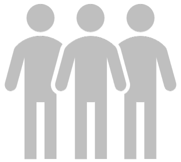
HIPRA

Strategies against ETEC and VTEC

Reduce number of pathogenic *E. coli*

Increase resistance of animals to infection

Nutrition



Management
Facilities

Immunity

Immunity against ETEC and VTEC

Reduce number of pathogenic *E. coli* and increase resistance of animals

Vaccination

- Maternal vaccination (for Neonatal diarrhea ex. F4(K88)
- Live oral nontoxigenic F4(K88) and F18 *E.coli* vaccines (PWD)
- Vt2e (Stx2e) toxoid vaccines (ED)

Oral antibodies

- Oral powdered egg yolk from F4(K88) and F18 immunized hens

Selection

- Genetic selection of F4(K88) and F18 resistant animals

Immunity against VTEC

Vaccination to increase resistance of animals

1. Ingestion of VTEC

2. Colonization small intestine (receptors in jejunum & ileum)

- ~~ETEC:F4~~
- **ETEC:F18** - age dependant (+10 days?/+20 days?) → 3 weeks ↑
  - cause disase slowly (after 5-7 days)
  - late-lactation and PWD

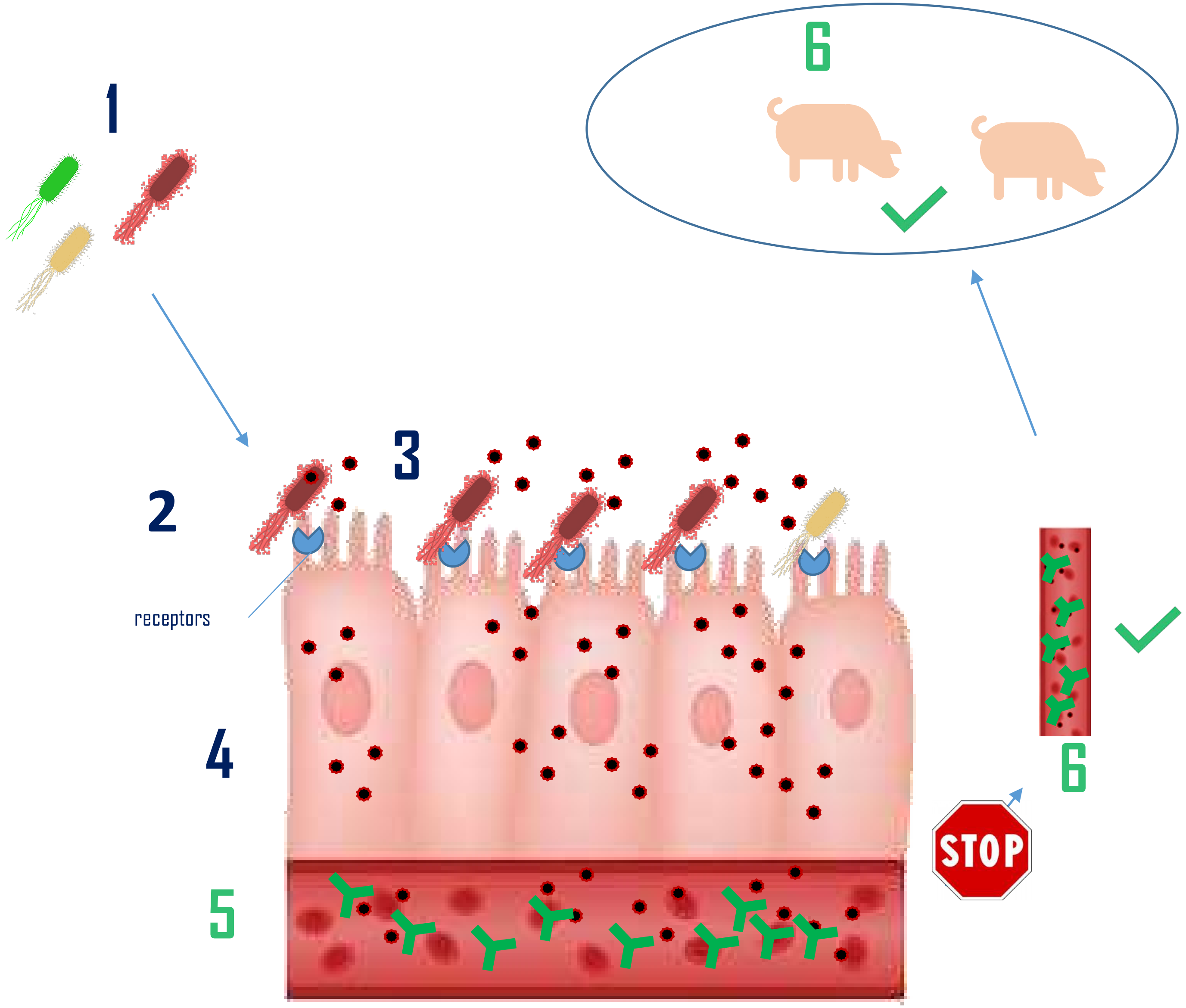
3. Production of verotoxins (Vt2e/Stx2e)

4. Transport of toxins to circulation

5. Antibodies neutralize the toxin

6. NO Affection to blood vessels

6. Healthy piglets NO edema, ataxia and death



Immunity against VTEC

Vaccination to increase resistance of animals

Animal and Veterinary Sciences
2018; 6(6): 95-101
http://www.sciencepublishinggroup.com/j/avs
doi: 10.11648/j.avs.20180606.11
ISSN: 2328-5842 (Print); ISSN: 2328-5850 (Online)
SciencePG Science Publishing Group

A Multicenter, Randomized Field Trial on the Efficacy and Safety of VEPURED®, A New Vaccine Against Edema Disease in Pigs

Eva Perozo[†], Joaquim Mallorquí[†, *], Ainhoa Puig, David Sabaté, Laura Ferrer-Soler, Ricard March

Trial in 4 commercial farms with ED disease

Mortality

Farm	Treatment	Number of pigs (n)	Number of pigs that died due to Edema Disease (%)	
3	Placebo	120	7 (7)	
	Vepured	121	0 (0)	
4	Placebo	180	6 (3.3)	
	Vepured	299	1 (0.3)	
All	Placebo	643	26 (4.0)	(*P* < .001)
	Vepured	764	2 (0.3)	

*Overall comparison p value for Generalized Linear mixed model with binary response and Farm as random effect. Results are statistically significant if the P value <.05.

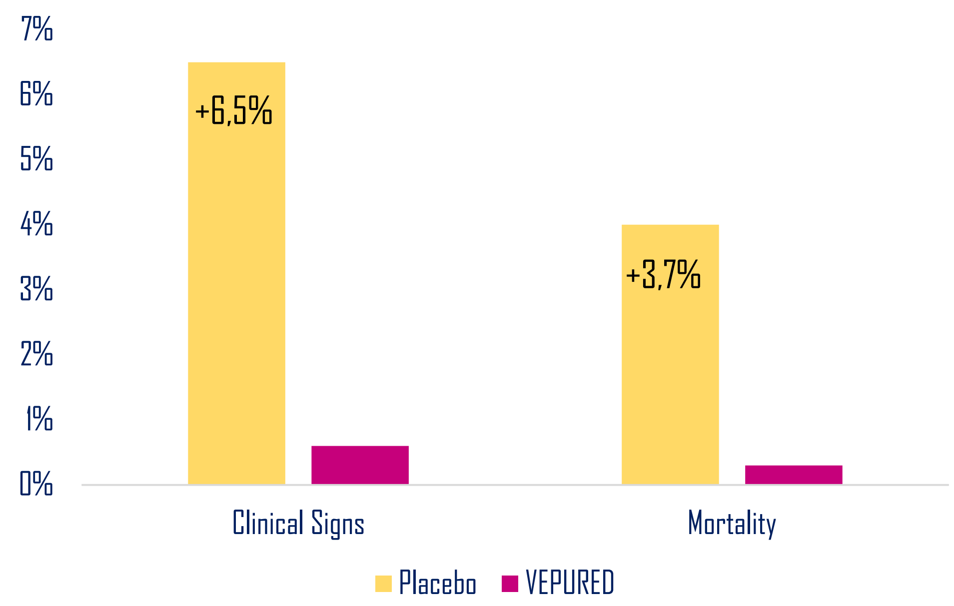
Clinical signs

Table 5. *Summary of animals showing Edema Disease Clinical Signs.*

Farm	Treatment	Number of pigs (n)	Number of pigs with Edema Disease Clinical Signs (%)	
1	Placebo	223	8 (3.6)	
	Vepured	224	1 (0.4)	
2	Placebo	120	7 (5.8)	
	Vepured	120	0 (0)	
3	Placebo	120	11 (9.2)	
	Vepured	121	0 (0)	
4	Placebo	180	16 (8.9)	
	Vepured	299	4 (1.3)	
All	Placebo	643	42 (6.5)	(*P* < .001)
	Vepured	764	5 (0.6)	

Overall comparison P value for Generalized Linear mixed model with binary response and Farm as random effect. Results are statistically significant if the P value <.05.

VEPURED® vs PLACEBO



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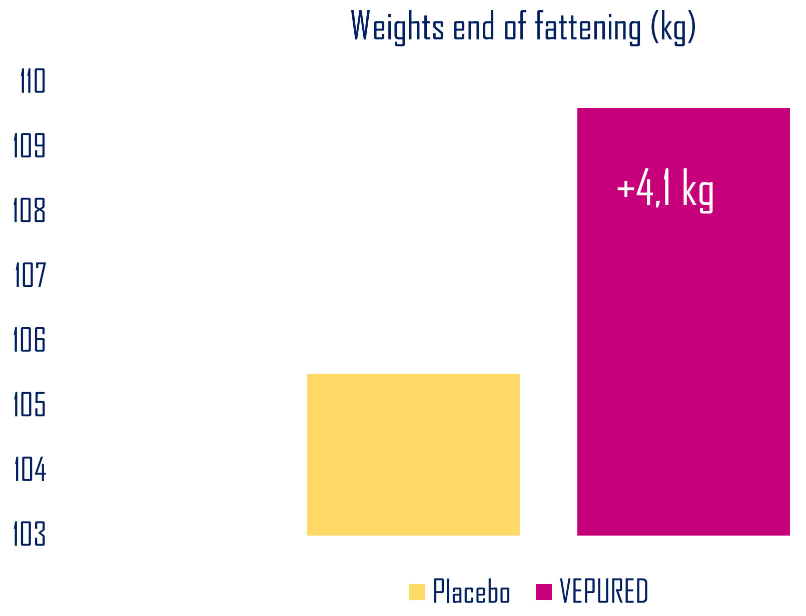
VEPURED® vs PLACEBO

Productive performance (weight)

Table 6. Evolution of animal weights in farms with clinical Edema Disease (Mean ± SD).

Farm	Treatment	d-1	d28	d42	d115	End of fattening
1	Placebo	2.26 ± 0.54	8.66 ± 1.52	13.98 ± 2.61	64.69 ± 11.2	101.44 ± 15.24
	Vepured	2.29 ± 0.58	8.62 ± 1.81	14.01 ± 3.15	66.69 ± 10.99	105.42 ± 13.76
2	Placebo	2.04 ± 0.45	8.87 ± 1.73	13.87 ± 2.66	62.90 ± 9.07	109.84 ± 11.12
	Vepured	2.05 ± 0.45	9.20 ± 1.78	14.25 ± 2.42	65.84 ± 7.92	113.27 ± 11.89
3	Placebo	1.82 ± 0.46	6.5 ± 1.35	14.61 ± 2.71	59.42 ± 9.55	97.67 ± 13.63
	Vepured	1.84 ± 0.5	7.23 ± 2.01	14.69 ± 3.27	62.47 ± 9.59	101.46 ± 12.96
4	Placebo	1.95 ± 0.37	7.05 ± 1.18	9.57 ± 2.01	57.22 ± 8.5	110.93 ± 13.77
	Vepured	1.98 ± 0.37	6.93 ± 1.16	10.47 ± 1.85	60.27 ± 9.17	115.45 ± 13.60
All	Placebo	2.01 ± 0.47	7.71 ± 1.69	12.67 ± 3.28	60.62 ± 9.96	105.54 ± 14.81
	Vepured	2.03 ± 0.49	7.77 ± 1.82	13.04 ± 3.21	63.5 ± 9.81	109.64 ± 14.35
	P value*	0.584	0.799	0.009	< .001	< .001

SD: standard deviation.
* P values for overall group comparison at fixed times using a Linear mixed model with farm as a random effect. Results are statistically significant if the P value <.05.



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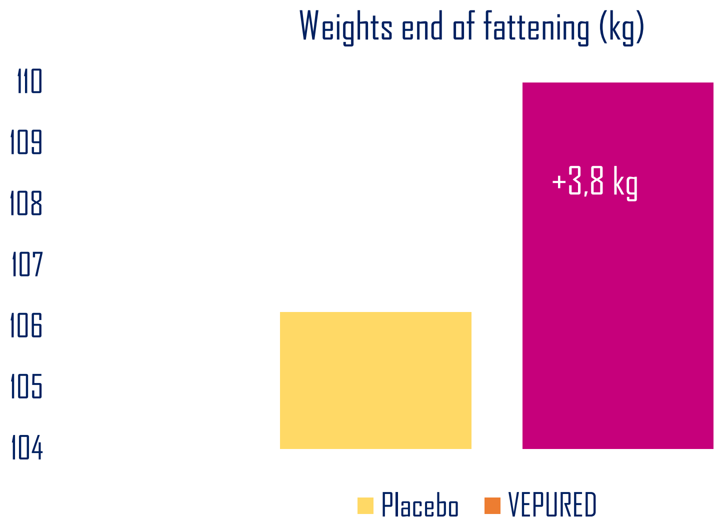
Trial in 1 commercial farm with Subclinical Edema Disease

VEPURED® vs PLACEBO

Productive performance (weight)

However, body weight was higher in the vaccinated group than in the placebo group on day 115 (58.49 kg vs 55.27 kg) and at end of fattening (110.06 kg vs 106.24 kg).



HIPRA

To sum up

Reduce number of pathogenic *E. coli*

Increase resistance of animals to infection

Nutrition

Management Facilities

Immunity

To sum up

Reduce number of pathogenic *E. coli*

Increase resistance of animals to infection

Nutrition

Water

Ingredients

Feed supplements

Management Facilities

Hygiene

Facilities & environment

Management

Water

Immunity

Vaccination

Oral antibodies

Genetic selection

Punti chiave per il controllo delle colibacillosi

Keys for controlling colibacillosis with restricted use of antimicrobials

Emili Barba Vidal, DVM, PhD
Corporate Brand Manager
Digestive and Respiratory Range
Swine Business Unit