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猪消化道疾病国际研讨会
International Pig Digestive Diseases Symposium

Prevention and control of ileitis with antimicrobials: Pro/Con
用抗菌剂预防和控制回肠炎的利与弊

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LI circulation problem in swine herds
猪群中胞内劳森菌传播的问题

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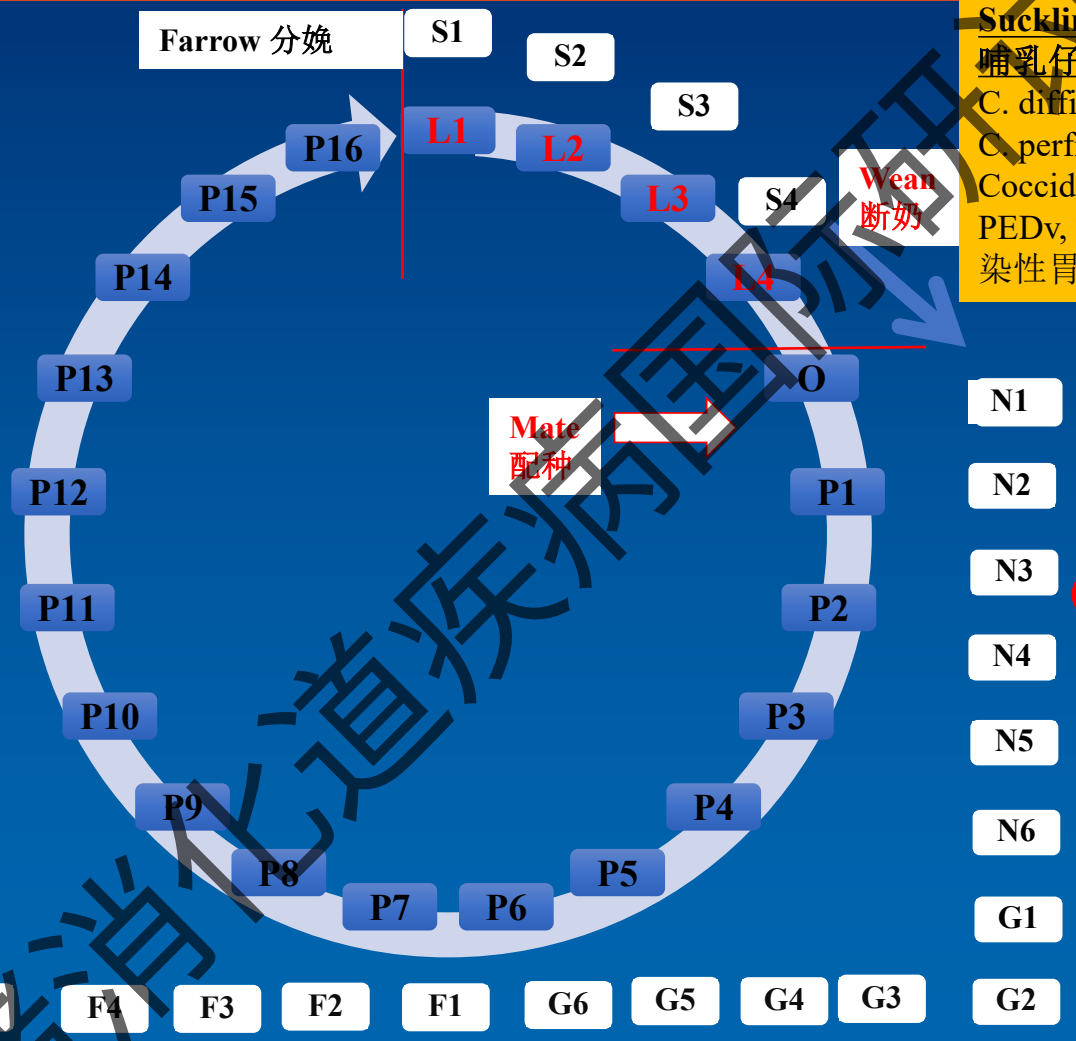
Common enteric diseases in swine production
养猪生产中常见的肠道疾病

Sows/gilts:
经产母猪/后备母猪：
PEDv
TGEv
Gastric Ulcer 胃溃疡
Ileitis 回肠炎
Swine dysentery猪痢疾
Torsion肠扭转



Suckling piglets:
哺乳仔猪
C. difficile Ileitis 艰难梭菌、回肠炎
C. perfringens 产气荚膜梭菌
Coccidiosis, E. coli 球虫病、大肠杆菌
PEDv, TGEv, ROTAv 猪流行性腹泻病毒（PEDV）、传染性胃肠炎病毒（TGEV）和轮状病毒（ROTAv）

Nursery pigs
保育猪
E. Coli
大肠杆菌
Ileitis
回肠炎
B. hyodysenteriae
猪痢疾密螺旋体
TGEv, PEDv
传染性胃肠炎病毒、猪流行性腹泻病毒
Trichuris
猪鞭虫

Growers/Finishers: Ileitis, Swine dysentery, Salmonellosis, Ascaris, Campylobacter, Balantidiasis, PMWS, Gastric ulcer
生长/育肥猪：回肠炎、猪痢疾、沙门氏菌病、蛔虫病、弯曲杆菌、结肠小袋纤毛虫病、断奶仔猪多系统衰竭综合征、胃溃疡

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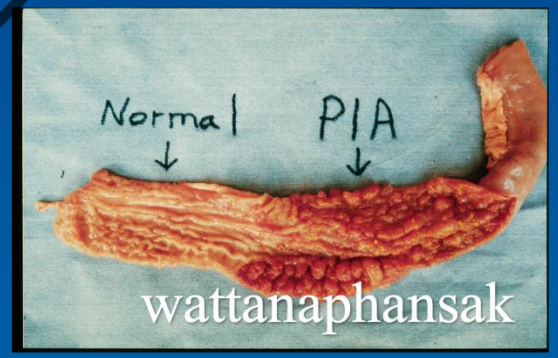
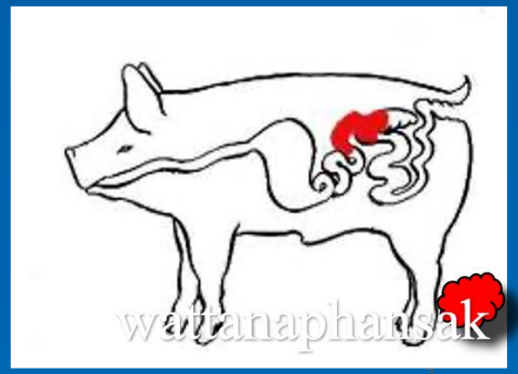
Proliferative enteropathy (PE)
增生性回肠炎（PE）

- An important enteric disease in grower and finisher pigs
  生长猪和育肥猪的重要肠道疾病
- Characterized by thickening of distal part of small intestine and proximal part of large intestine
  其特点是小肠远端和大肠近端增厚
- Common names:
  常见名称：
  - Ileitis
    回肠炎
  - Porcine intestinal adenomatosis (PIA)
    猪肠腺瘤病（PIA）
  - Proliferative hemorrhagic enteropathy (PHE)
    增生性出血性回肠炎（PHE）
- It is caused by *Lawsonia intracellularis*
  由胞内劳森菌引起





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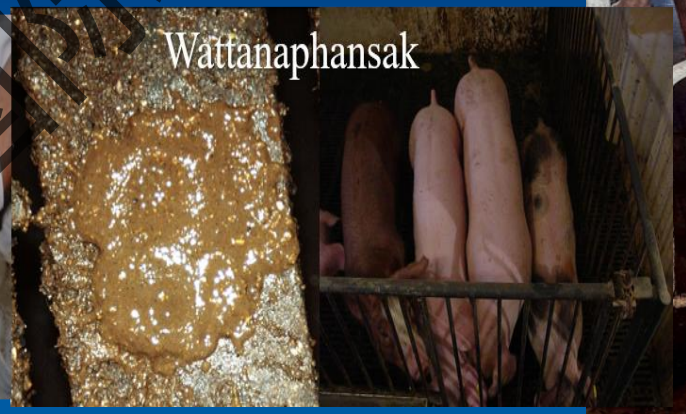
Proliferative enteropathy (PE)
增生性回肠炎

- Three forms of clinical manifestations in pigs
  猪的三种临床表现形式
  - Proliferative hemorrhagic enteropathy (PHE)
    增生性出血性肠炎
    - Acute form 急性型
    - Bloody diarrhea 出血性腹泻
    - Sudden death in adult pigs 成年猪猝死
  - Porcine intestinal adenomatosis (PIA)
    猪肠腺瘤病（PIA）
    - Chronic form: Usually found in younger pigs
      慢性形式：通常发现在小日龄猪身上
    - Chronic diarrhea 慢性腹泻
    - Abnormal proliferation of small intestine 小肠异常增生
  - Subclinical ileitis
    亚临床回肠炎
    - Slow growth 生长缓慢
    - No sign of diarrhea or not detectable 没有腹泻的病征或不易检测到
    - Gross lesions: not easily to recognize 肉眼病变：不易识别



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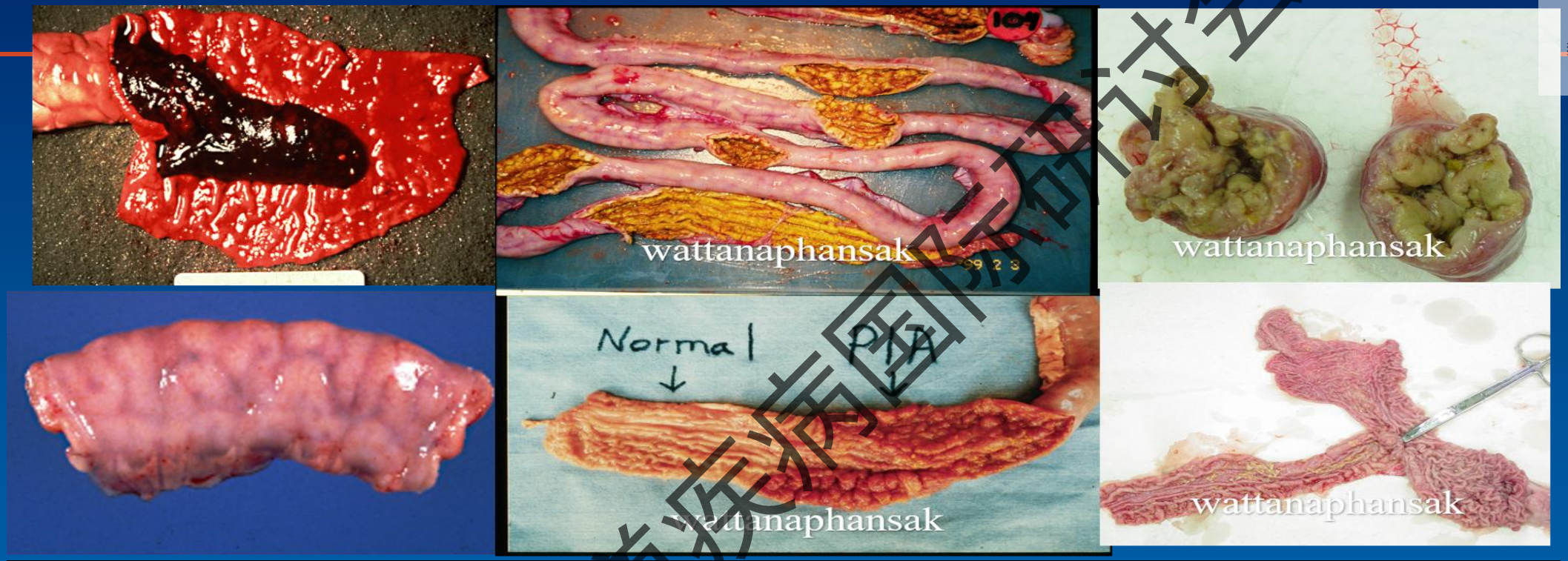

Disease 疾病	Diagnostic methods 诊断方法	Organs 器官
Ileitis 回肠炎	1. Bacterial culture (Not practical) 细菌培养（不实用） 2. PCR: conventional or real-time PCR PCR：常规PCR或实时PCR 3. Immunohistrochemistry 免疫组织化学 4. Serological assay: IPMA, IFAT, ELISA 血清学测定：免疫过氧化物酶单层含量测定（IPMA）、间接免疫荧光抗体测定（IFAT）、酶联免疫吸附试验（ELISA）	Small intestine especially Ileum, feces 小肠，特别是回肠，粪便

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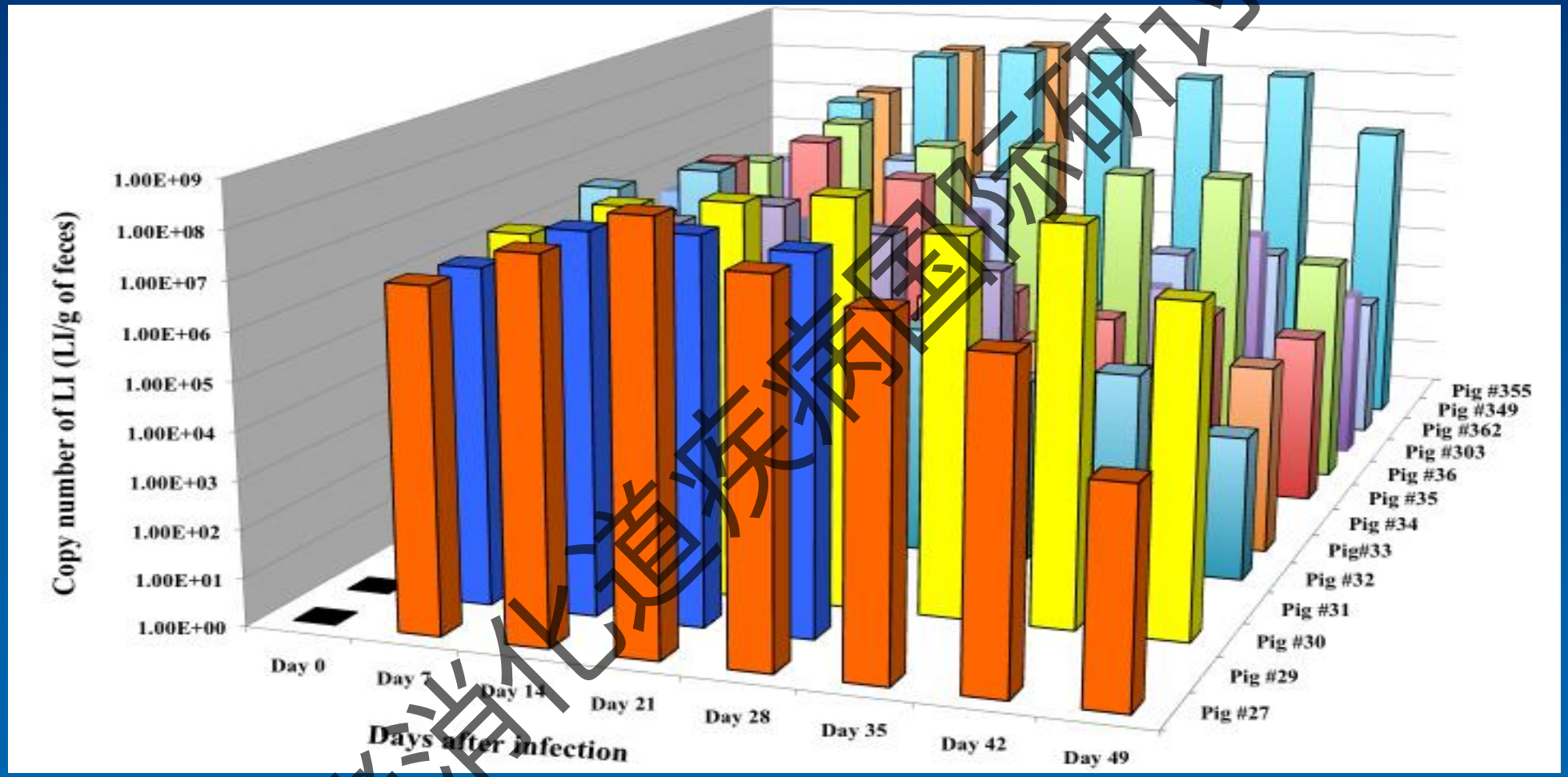
Dynamic of fecal sheding of LI during 49 days of experimental challenge with LI pure culture
用胞内劳森菌纯培养物进行为期49天的实验攻毒期间，胞内劳森菌的粪便排毒动态



Wattanaphansak et al., IPVS2010

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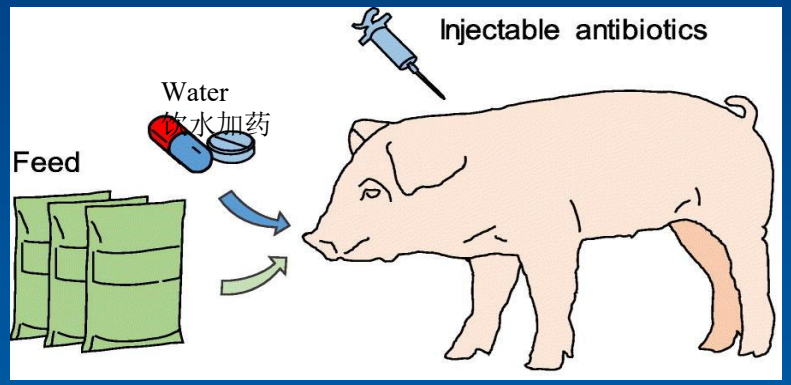
Treatment and control of PE
回肠炎的治疗和控制

- Antimicrobials therapy- Clear bacteria inside pigs
  抗菌剂疗法——清除猪体内的细菌
  - Feed antimicrobials 饲料加抗菌剂
  - Water antimicrobials 饮水加抗菌剂
  - Injectable antimicrobials 注射用抗菌剂



- Vaccinations-modified live/killed vaccine-active antibody
  疫苗接种——减毒活疫苗/灭活疫苗——活性抗体
- Gut homogenate/ pure culture inoculum+antimicrobials
  肠道匀浆/纯培养接种物+抗菌剂
- Passive egg antibodies/ Pre, Pro, Postbiotics, immune stimulant feed supplements- gut health
  被动卵黄抗体/益生元、益生菌、后生元及免疫刺激饲料添加剂——改善肠道健康
- Disinfections- Clear bacteria in the environment
  消毒——清除环境中的细菌

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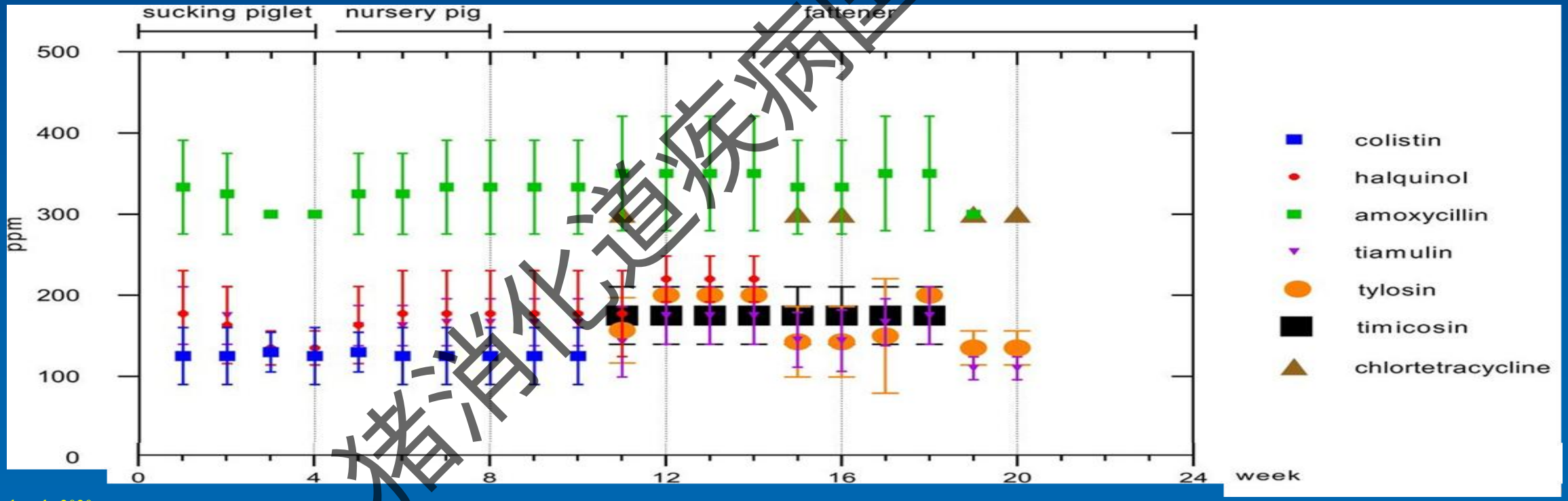
Use of antibiotics in relation to common diseases and management
抗生素使用与常见疾病和管理

- Amoxicillin and tiamulin were commonly recommended for use at all stages 对于所有生产阶段，通常建议使用阿莫西林和泰妙菌素
- Halquinol and colistin were recommended for suckling piglets and nursery pigs for prevention of enteric infection
  对于哺乳仔猪和保育猪，通常推荐使用哈喹诺和黏菌素，以预防肠道感染
- Tylosin, tilmicosin, and chlortetracycline were recommended for fatteners 至于育肥猪，通常建议使用泰乐菌素、替米考星和金霉素
- The duration of antibiotic use was commonly about 4 to 6 weeks 抗生素使用的持续时间通常约为4到6周



Lekagul et al., 2020

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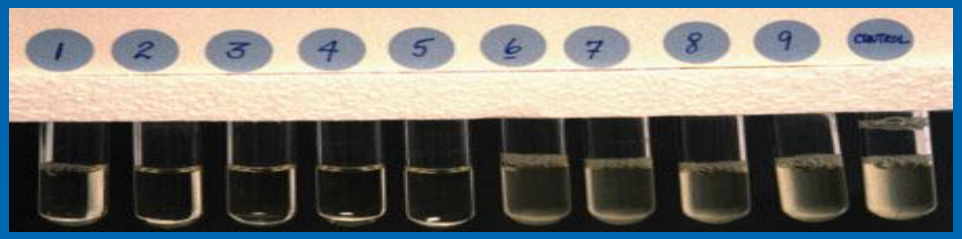
Antimicrobials control of PE-Con
用抗菌剂控制增生性肠炎的弊端

- Little information is available about the *in vitro* activity of antimicrobials against LI.
  目前关于抗菌剂对胞内劳森菌的体外活性了解甚少
  - Primary isolation from infected intestine is extremely difficult 从受感染的肠道中进行初级分离极为困难
  - Less than 25 isolates worldwide 全球范围内的分离株不到25种
  - Standard antimicrobial tests are not applicable 标准抗菌剂测试不适用
  - Tissue culture system was used---Complicated system曾采用组织培养系统——复杂的系统
- Antimicrobial selections based on *in vitro* results but impossible to obtain in time during the PE outbreak
  根据体外的结果选择抗菌剂，但在增生性肠炎暴发期间无法及时获取



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Antimicrobials control of PE-Con
用抗菌剂控制增生性肠炎的弊端

- Little information on MIC against LI is available
  关于胞内劳森菌的最小抑制浓度（MIC）的信息有限
  - 3 strains of LI from UK (McOrist et al., 1995) 来自英国的3株胞内劳森菌菌株（McOrist等，1995）
    - Most active: Penicillin, Erythromycin, Difloxacin, Virginiamycin 活性最高：青霉素、红霉素、二氟沙星、维吉尼霉素
    - Moderate active: Tiamulin, Lincomycin, Tilmicosin, Tylosin, Chlortetracycline 中等活性：泰妙菌素、林可霉素、替米考星、泰乐菌素、金霉素
    - Least active: Aminoglycosides, Ceftiofur, Bacitracin 活性最低：氨基糖苷类、头孢噻呋、杆菌肽
  - 10 strains of LI, 6 from USA, 4 from EU (Wattanaphansak et al., 2009)
    10株胞内劳森菌菌株，其中6株来自美国，4株来自欧盟（瓦塔纳攀萨克等，2009）
    - Most active: Carbadox, Tiamulin, Valnemulin 活性最高：卡巴氧、泰妙菌素、沃尼妙林
    - Moderate active: Tylosin, Chlortetracycline 中等活性：泰乐菌素、金霉素
    - Least active: Lincomycin 活性最低：林可霉素
  - 2 strains of LI from Korea, (Yeh et al, 2011)
    来自韩国的2株胞内劳森菌菌株（Yeh等，2011）
    - Most active: Tylosin, Tilmicosin, Carbadox 活性最高：泰乐菌素、替米考星、卡巴氧
    - Moderate active: Tiamulin, Ampicillin, Penicillin, Enrofloxacin, Chlortetracycline 中等活性：泰妙菌素、氨苄西林、青霉素、恩诺沙星、金霉素
    - Least active: Lincomycin, spectinomycin, Bacitracin, Aminoglycosides活性最低：林可霉素、壮观霉素、杆菌肽、氨基糖苷类

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Antimicrobials control of PE-Con
用抗菌剂控制增生性肠炎的弊端

Origin of LI 胞内劳森菌的来源	Strains of LI 菌株	No. of Passages 传代次数	Collection Year 采集年份
USA 美国	VPB4	165-166	1991
USA 美国	PHE/MN1-00	169-170	2000
USA* 美国*	KKumn04	17-18	2004
USA* 美国*	NWumn05	21-22	2005
USA* 美国*	DBumn-06	8-9	2006
USA* 美国*	47216-06	7-8	2006
Denmark 丹麦	D15340	19-20	1998
United Kingdom 英国	LR139/5/83	14-15	1983
United Kingdom 英国	916/91	16-17	1991
United Kingdom 英国	963/93	35-36	1993

- All isolates were tested twice
  所有分离株均进行了两次测试
- *New isolates *新分离株 (Wattanaphansak et al, 2009)

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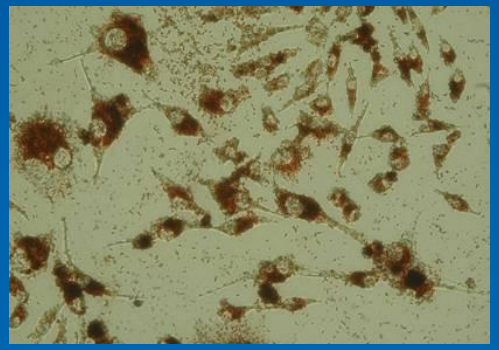
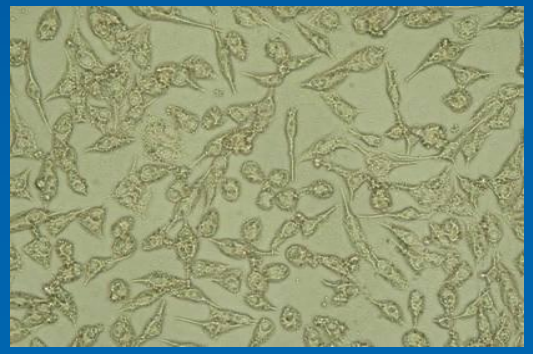
Antimicrobials control of PE-Con
用抗菌剂控制增生性肠炎的弊端

- Antimicrobial selections based on *in vitro* results 根据体外结果选择抗菌剂
- MICs = the lowest concentration that inhibited 99% of LI growth indicated by heavily infected cells (HIC), compared to the untreated controls
  最小抑菌浓度= 与未处理的对照组相比，能抑制重度感染细胞中99%胞内劳森氏菌生长的最低浓度
- Extracellular MICs = the effect of antimicrobial on LI prior to infection of intestinal cells
  细胞外最小抑菌浓度= 抗菌剂在肠道细胞感染前对胞内劳森氏菌的作用效果
- Intracellular MICs = the effect of antimicrobial on LI after infecting the intestinal cells
  细胞内最小抑菌浓度= 抗菌剂在肠道细胞感染后对胞内劳森氏菌的作用效果

Extracellular MICs
细胞外最小抑菌浓度



Heavily infected cells
严重感染的细胞



Uninfected cells
未感染的细胞

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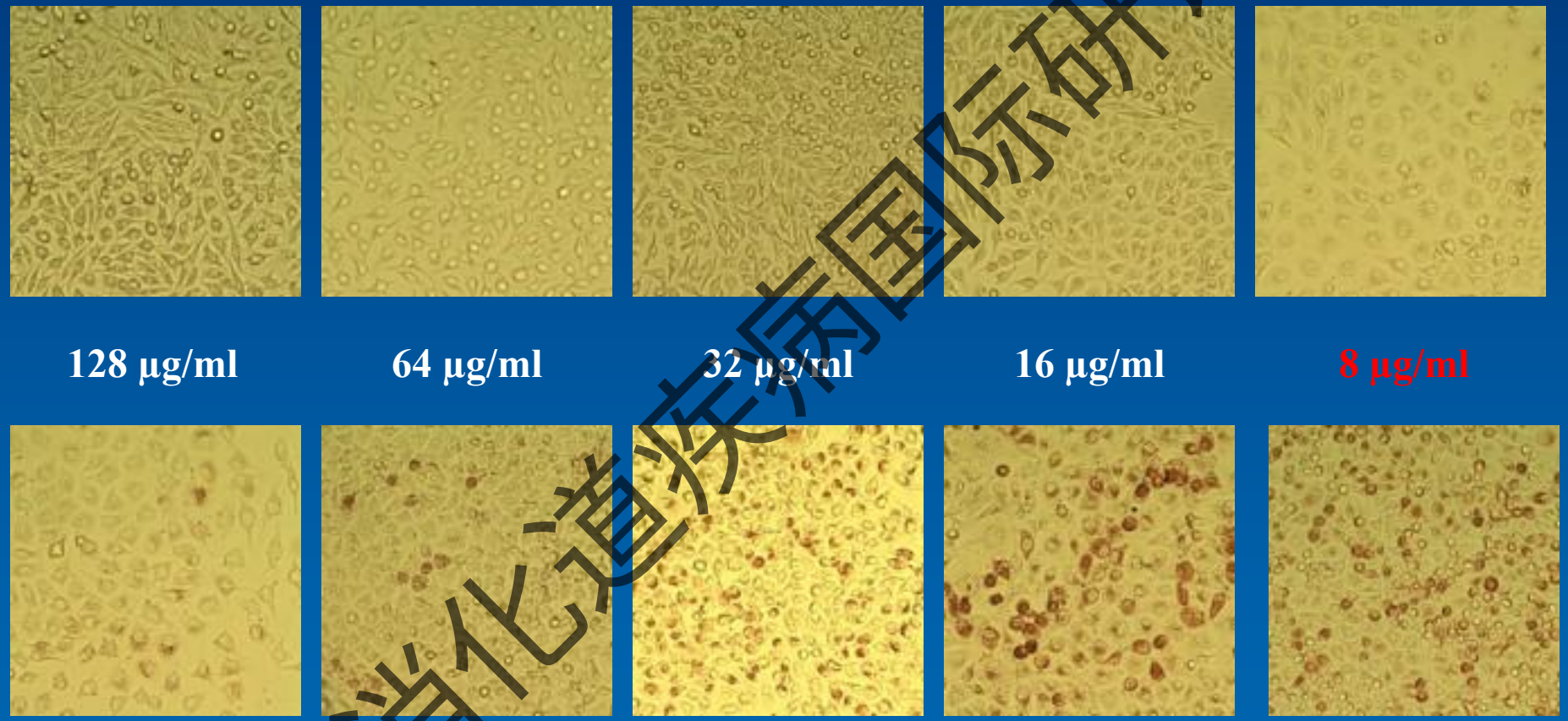
Antimicrobials control of PE-Con
用抗菌剂控制增生性肠炎的弊端

(Wattanaphansak et al, Vet Micro, 2009)



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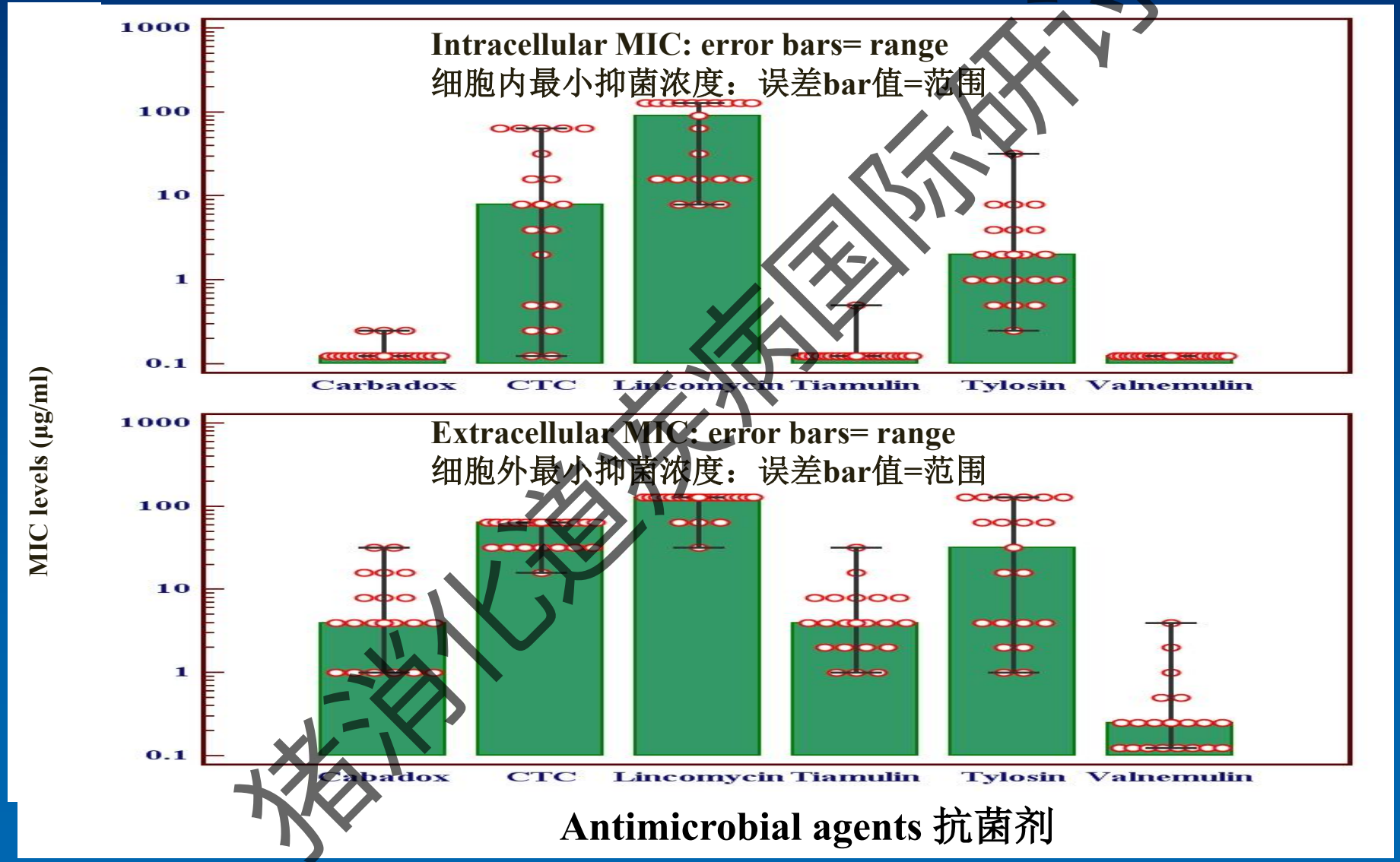
用抗菌剂控制增生性肠炎的弊端



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Antimicrobials control of PE-Con
用抗菌剂控制增生性肠炎的弊端

Isolate分离株	CUPHE01_SW13	CUPIA01_SW13	CUPIA02_SW13	BRPHE01_E5	BRPHE02_E8
Lesion 病变	PHE 增生性出血性回肠炎	PIA 猪肠道腺瘤病	PIA 猪肠道腺瘤病	PHE 增生性出血性回肠炎	PHE 增生性出血性回肠炎
Affected pig 受感染猪只	gilt 后备母猪	finisher 育肥猪	finisher 育肥猪	finisher 育肥猪	finisher 育肥猪
Clinical sign 临床症状	acute bloody diarrhea 急性出血性腹泻	found at slaughter house 发现于屠宰厂	found at slaughter house 发现于屠宰厂	acute bloody diarrhea 急性出血性腹泻	acute bloody diarrhea 急性出血性腹泻
Source 来源	Kanchanaburi, Thailand 泰国北碧府	Nakhon Pathom, Thailand 泰国佛统府	Nakhon Pathom, Thailand 泰国佛统府	Minas Gerais state 巴西米纳斯吉拉斯州	São Paulo state 巴西圣保罗州
100% HIC	passage 5 传代5次	passage 5 传代5次	passage 4 传代4次	passage 5 传代5次	passage 5 传代5次
Tested passage 受测代次	P6-P7	P8-P9	P5-P6	P13-P14	P13-P14
Collected year 采集年份	2013 2013	2013 2013	2012 2012	2011 2011	2011 2011

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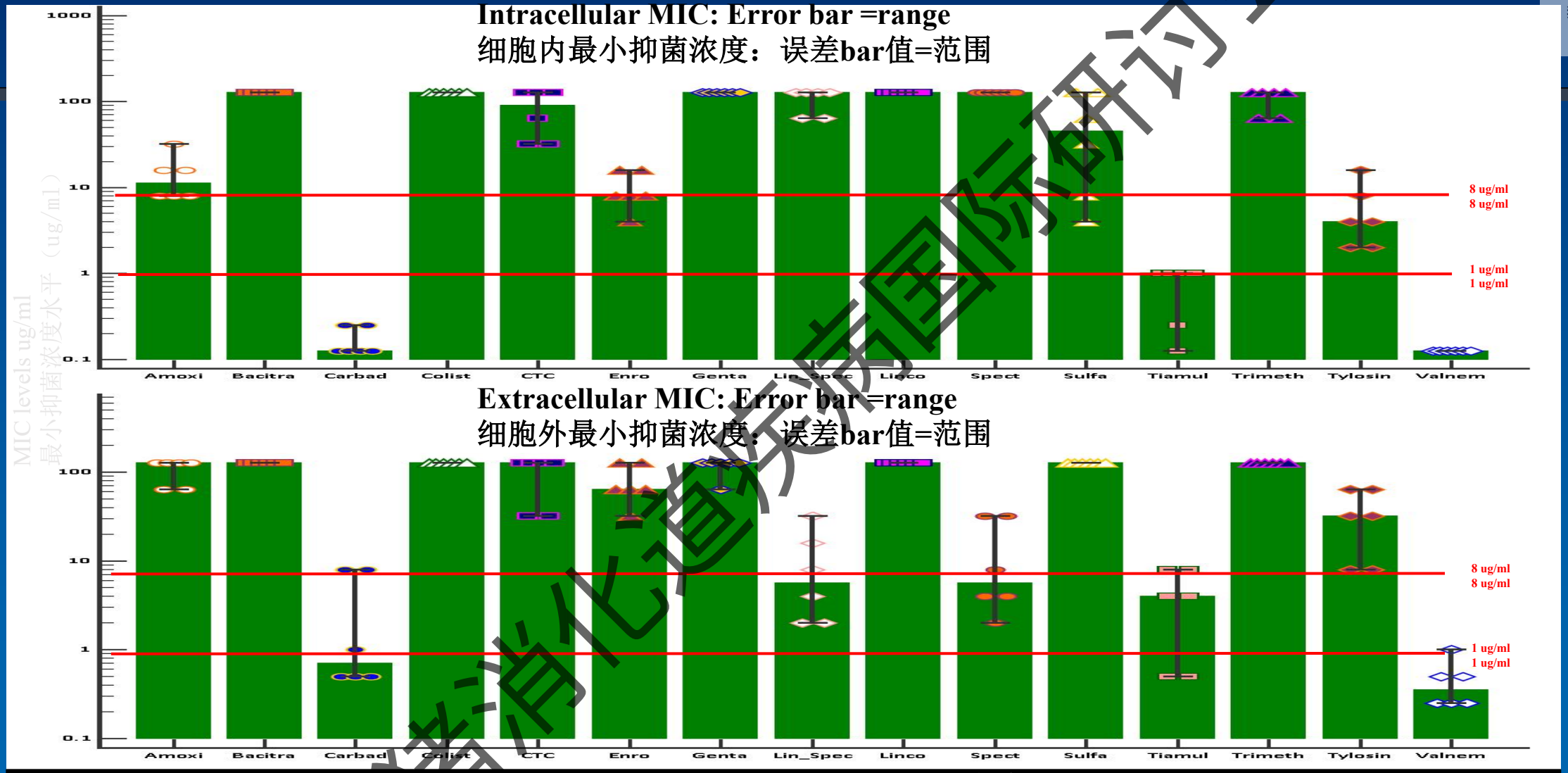
Antimicrobials control of PE-Thai
用抗菌剂控制增生性肠炎——泰国



Antimicrobial agents 抗菌剂

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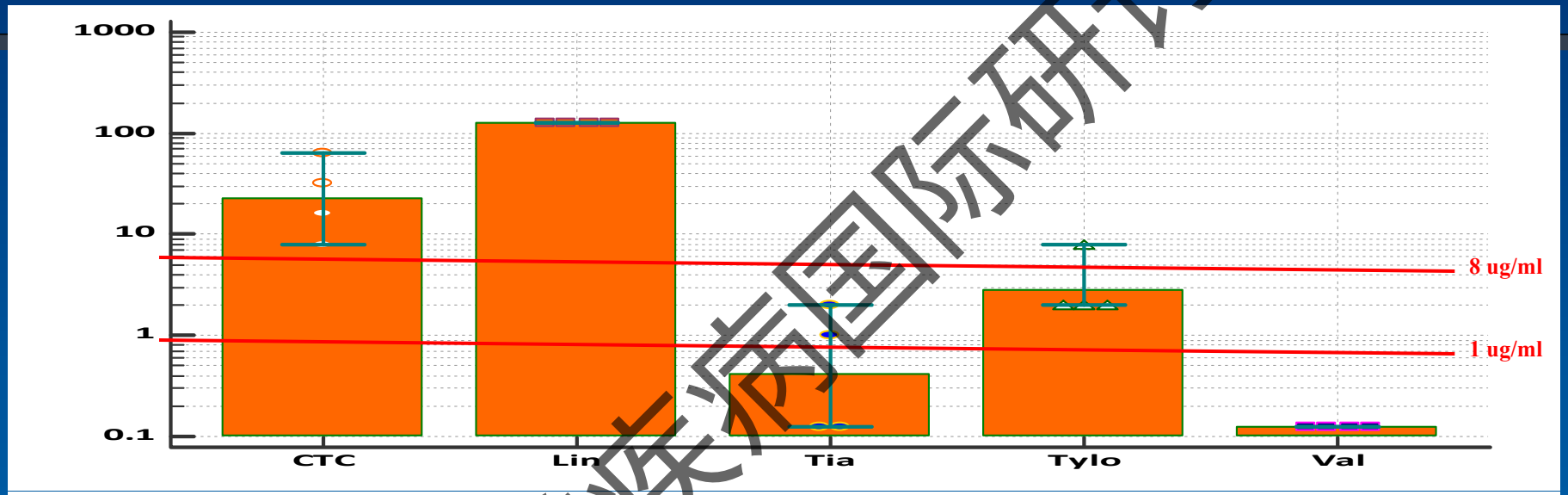
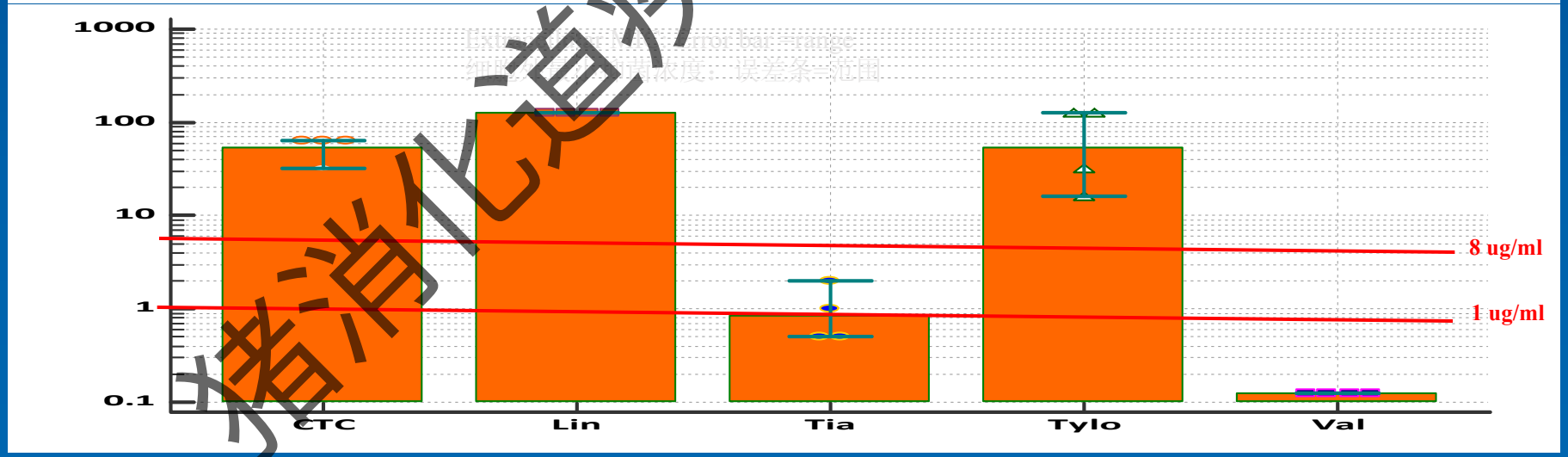
Antimicrobials control of PE-Bra
用抗菌剂控制增生性肠炎——巴西

Intracellular MIC: Error bar =range
细胞内最小抑菌浓度：误差bar值=范围





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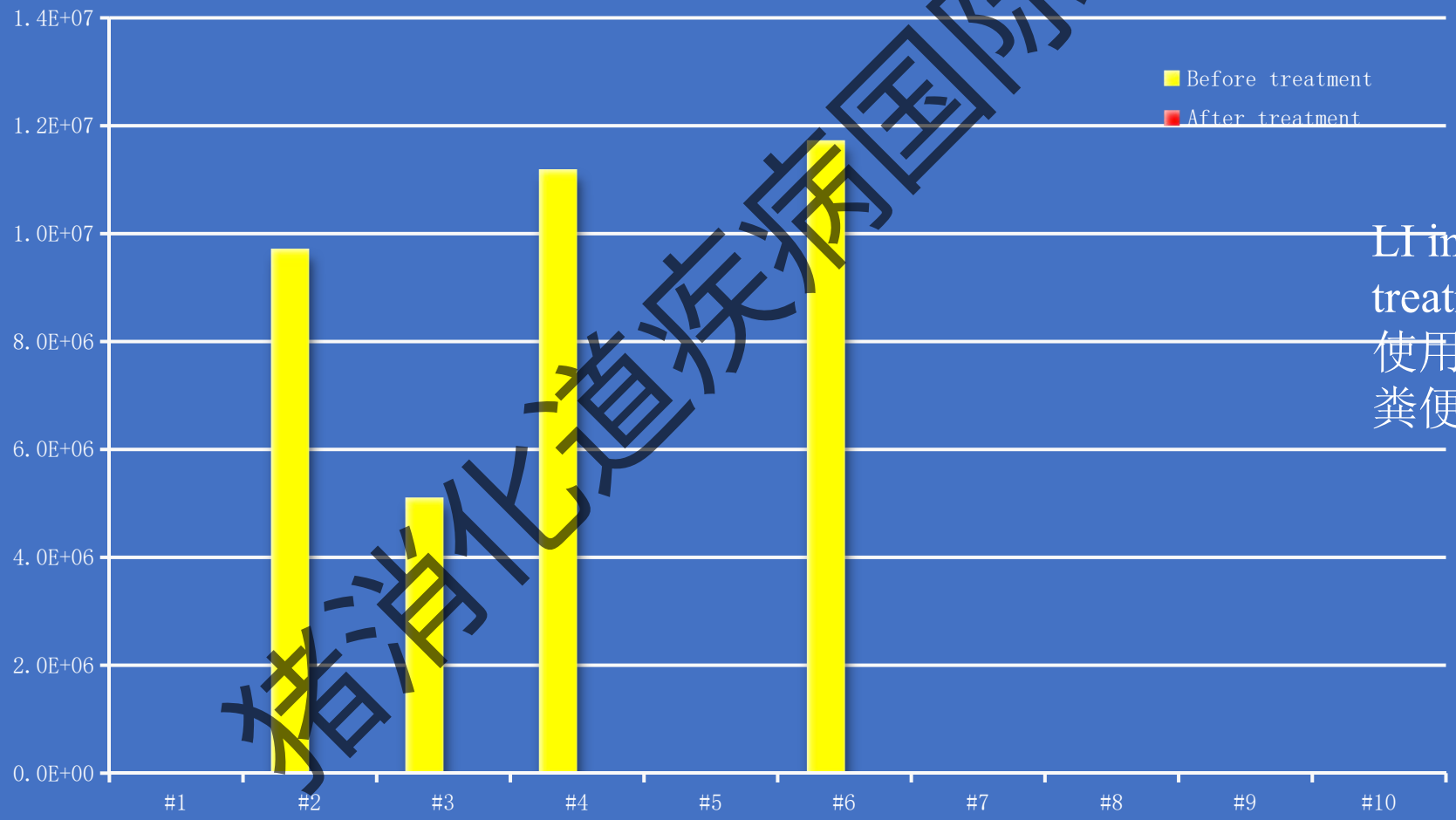
Antimicrobials control of PE-PRO
用抗菌剂控制增生性肠炎的优势

- The outbreak of PE can be controlled in short period of time and shedding of bacteria can be reduced through feces 增生性肠炎的暴发可以在短时间内得到控制，并且减少粪便中排出的细菌



LI in feces after treatment with tylosin
使用泰乐菌素治疗后粪便中的胞内劳森菌

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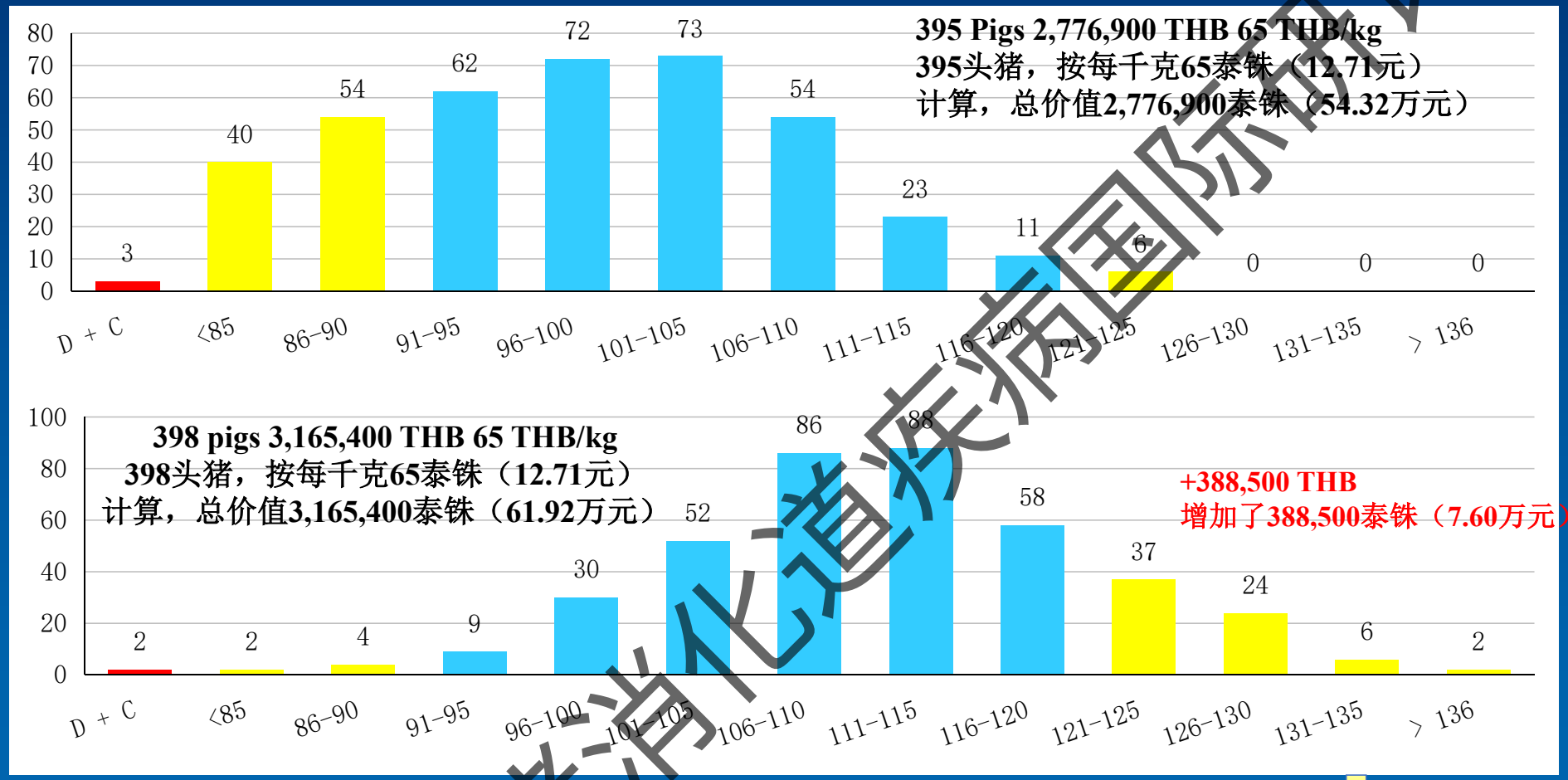
Frequency of weight out of finisher pigs before and after control ileitis with tylosin
用泰乐菌素控制回肠炎前后育肥猪的体重分布



Before Tx
治疗前

After Tx
治疗后

- Improved growth performances, ADG ↑ FCR ↓
  改善了生长性能，提高了日增重（ADG）和降低了料肉比（FCR）

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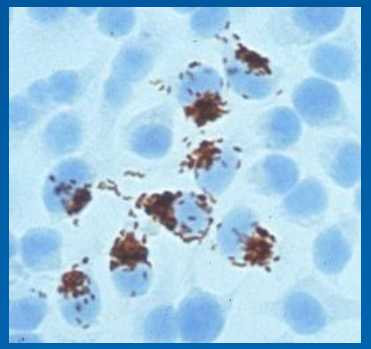
Antimicrobials control of PE-Con
用抗菌剂控制增生性肠炎的弊端

- At least 6 months- 1 year will take to determine the MIC results for LI
  至少需要6个月至1年的时间来确定胞内劳森菌的MIC结果

- Each strain of LI has a different antimicrobial susceptibility pattern
  每株胞内劳森菌菌株的抗菌药物敏感性模式都不同

- Thai LI isolates tended to have higher intracellular and extracellular MIC endpoint than the US, EU, Bra and Korean isolates
  泰国的胞内劳森菌分离株通常比美国、欧盟、巴西和韩国的分离株具有更高的细胞内和细胞外MIC终点
  - intensively used of high dosage of antimicrobials
    大量使用高剂量抗菌剂
  - Antimicrobials resistant pattern ???
    抗菌剂耐药模式？？？



- Decision making for selection of antimicrobials depend on previous information
  抗菌剂的选择决策依赖于先前的信息

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Control of ileitis with Antimicrobials
用抗菌剂控制回肠炎

Age
日龄

			30 %			10 %			-			20 %			60 %			90 %			100 %			100 %
0	1	2	3 4	5	6	7	8	9 10	11	12	13	14	15	16 17	18	19	20	21 22	23	24				

Early treatment, no immune responded, reinfection occurs
早期治疗，无免疫应答，再次感染

Balance infected animals, immune response developed, less proportion of reinfection
感染动物治疗时机恰当，产生免疫应答，再感染比例较低

Too late treatment, animal suffer from clinical signs
治疗太晚，动物有临床病征

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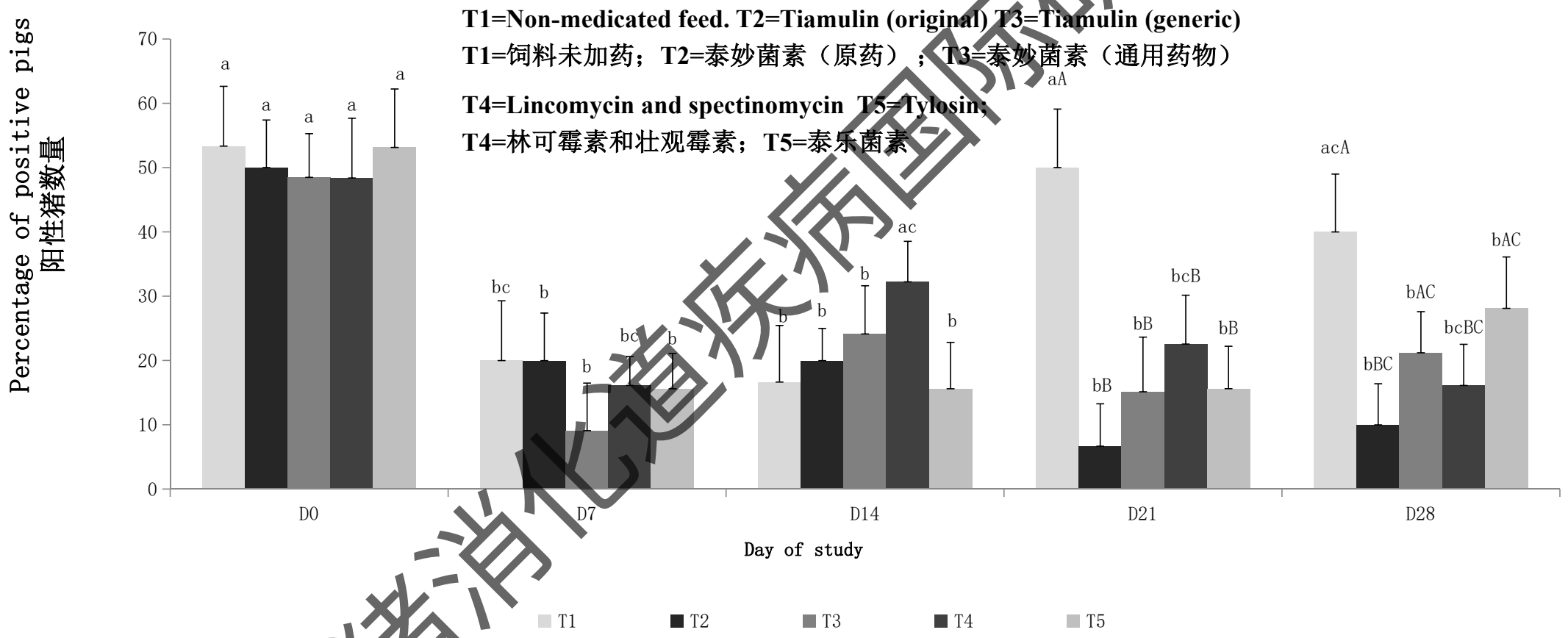
Antimicrobials can reduce number of positive pig and reduce bacterial shedding
抗菌剂可以减少阳性猪的数量并减少细菌排出



(Pramarn et al., APVS 2013)

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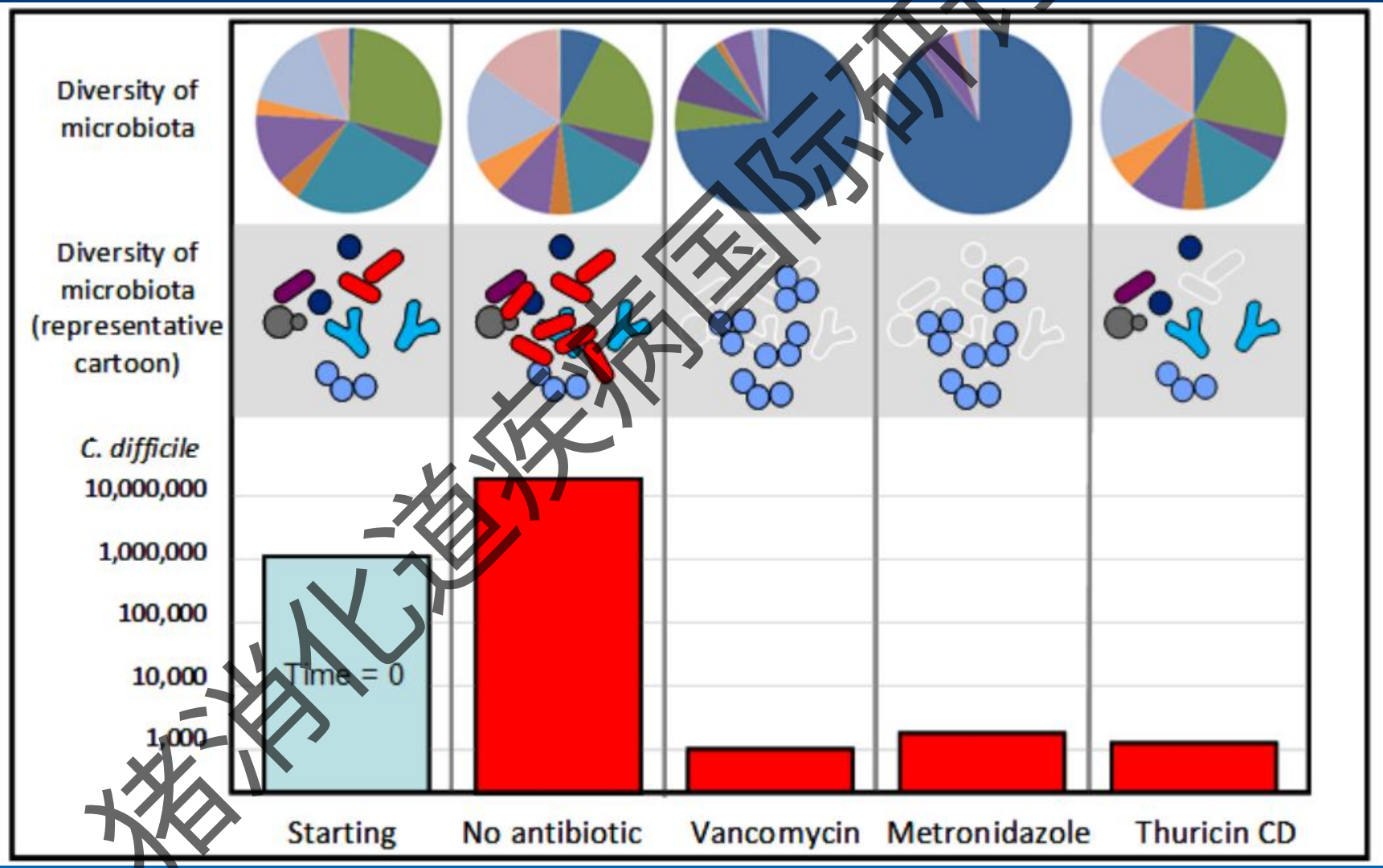
Impact of antimicrobials after 24 h on gut microbiome
24小时后抗菌剂对肠道菌群的影响

菌群多样性

菌群多样性
（代表性图示）

艰难梭菌



起始状态　无抗生素　万古霉素　甲硝唑　苏云金菌素CD

Cotter, 2012

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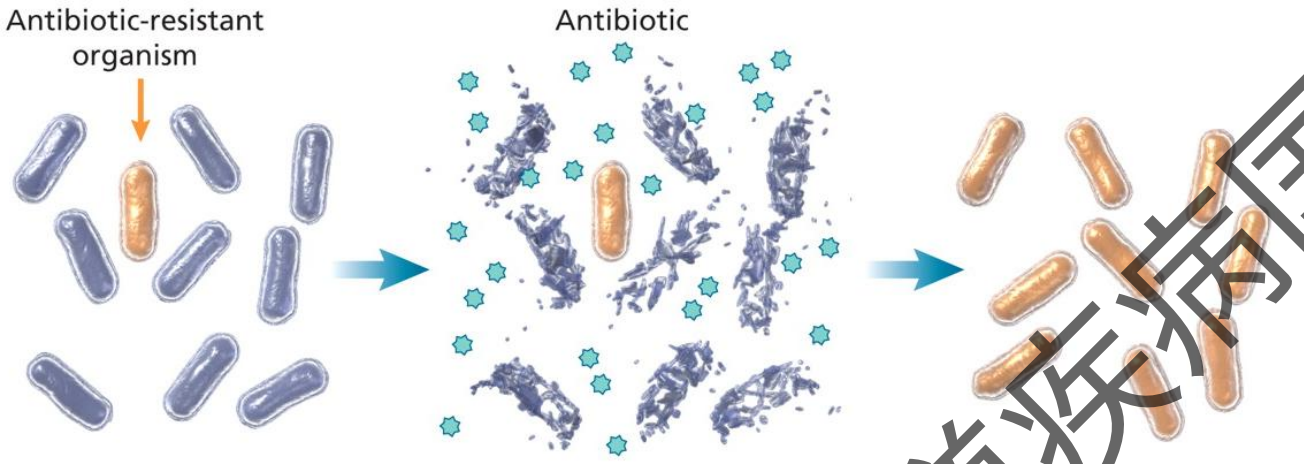
Disruption of gut microbiota and potential for dysbiosis
肠道菌群的紊乱及可能导致的菌群失调

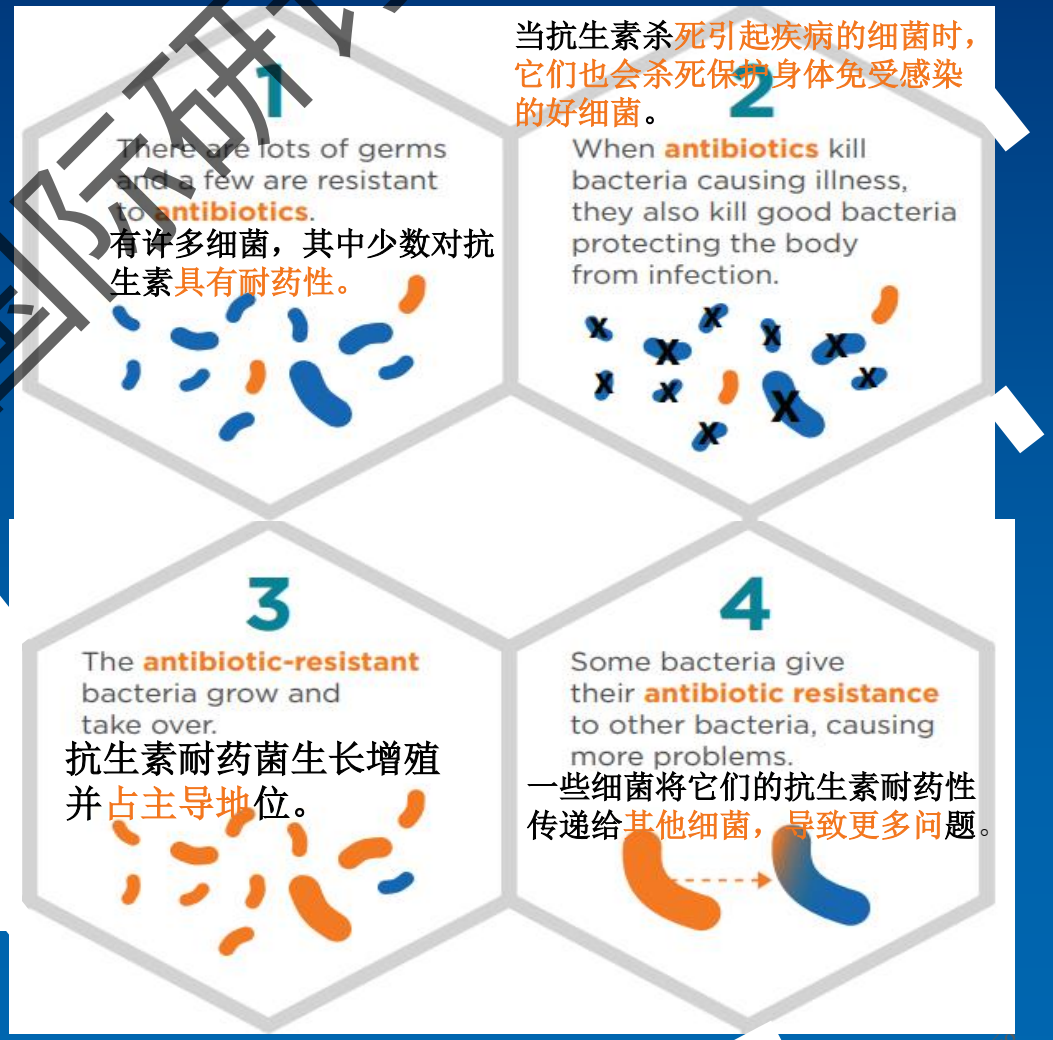
抗生素耐药菌　　抗生素



细菌群中含有一部分抗生素耐药菌。

在抗生素的作用下，易感菌株被杀死；耐药菌株存活下来。

耐药菌株增殖，并可能引发新的感染。



Mulvey, Simor, 2009

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Control summary with antimicrobials
用抗菌剂控制回肠炎的总结

Pro
优势

- **High Efficacy** and rapid action in reducing the severity of clinical signs and ileitis lesions
  高效和迅速的行动可减轻临床症状和回肠炎病变的严重程度
- Can control other pathogens at the same time 同时可以控制其他病原体
  - To obtain the best outcome 为了获得最佳效果
    - Antemortem tests need to be applied for identify time of infection 需要进行死前检测以确定感染时间
    - Selected the best time for using antimicrobials 选择使用抗菌剂的最佳时机
    - Making decision on which antimicrobials will be used (available in each region, cost, dosages) 决定使用哪种抗菌剂（考虑各地区供应量、成本、剂量）
    - Goal: pig developed natural immunity after antimicrobials removal
      目标：在停用抗菌剂后，猪能产生自然免疫力

Con
弊端

- Continuous using of antimicrobials, natural immunity will not develop → reinfection occurs
  持续使用抗菌剂，猪无法发展自然免疫力；会再次感染
- Use of antimicrobials changes the dynamics of infection 使用抗菌剂会改变感染的动态
- Disruption of gut microbiota: Leading to dysbiosis and secondary health issues 扰乱肠道菌群：导致菌群失调和次发健康问题

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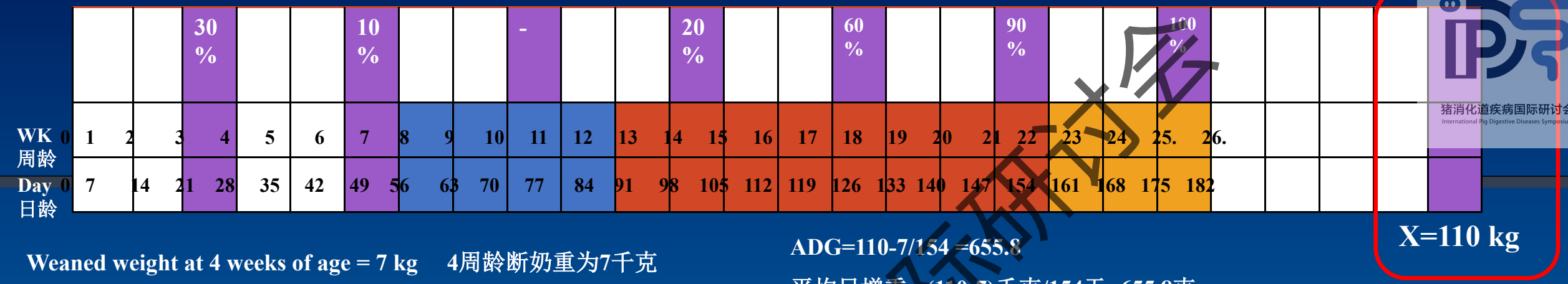

Weaned weight at 4 weeks of age = 7 kg　4周龄断奶重为7千克

Finisher weight at 26 weeks of age =110 kg　26周龄育成重为110千克

day of rasing pigs=161 days　养猪天数 = 161天

ADG=110-7/154 =655.8

平均日增重= (110-7)千克/154天=655.8克

ADG<650 " The lower ADG, ileitis is highly suspected "

平均日增重<650克 "平均日增重越低，越有可能患回肠炎"

Tx with. Antimicrobials
用抗菌剂进行治疗

Weaned weight at 4 weeks of age = 7 kg　4周龄断奶重为7千克

Finisher weight at 24 weeks of age =110 kg　24周龄育成重为110千克

day of rasing pigs=140 days　养猪天数 = 140天

ADG=110-7/140 =735.7

平均日增重=(110-7)千克/140天=735.7克

ADG>735.7 " The ADG is improved and ileitis is under controlled "

平均日增重>735.7克 "平均日增重有所提高，回肠炎得到了控制"

14 days save feeding cost (14x10CNY/day=140CNY/pig x 1,000,000 pigs/month = 140,000,000 CNY/month

14天节省饲料成本（14天×10元/天=140元/猪×100万头猪/月=1.4亿元/月）

How much you can save ???
你能节省多少钱?

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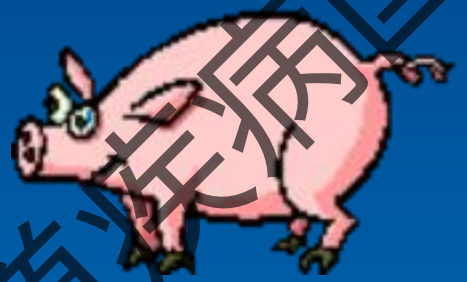
International Pig Digestive Diseases Symposium

Thank you
谢谢



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