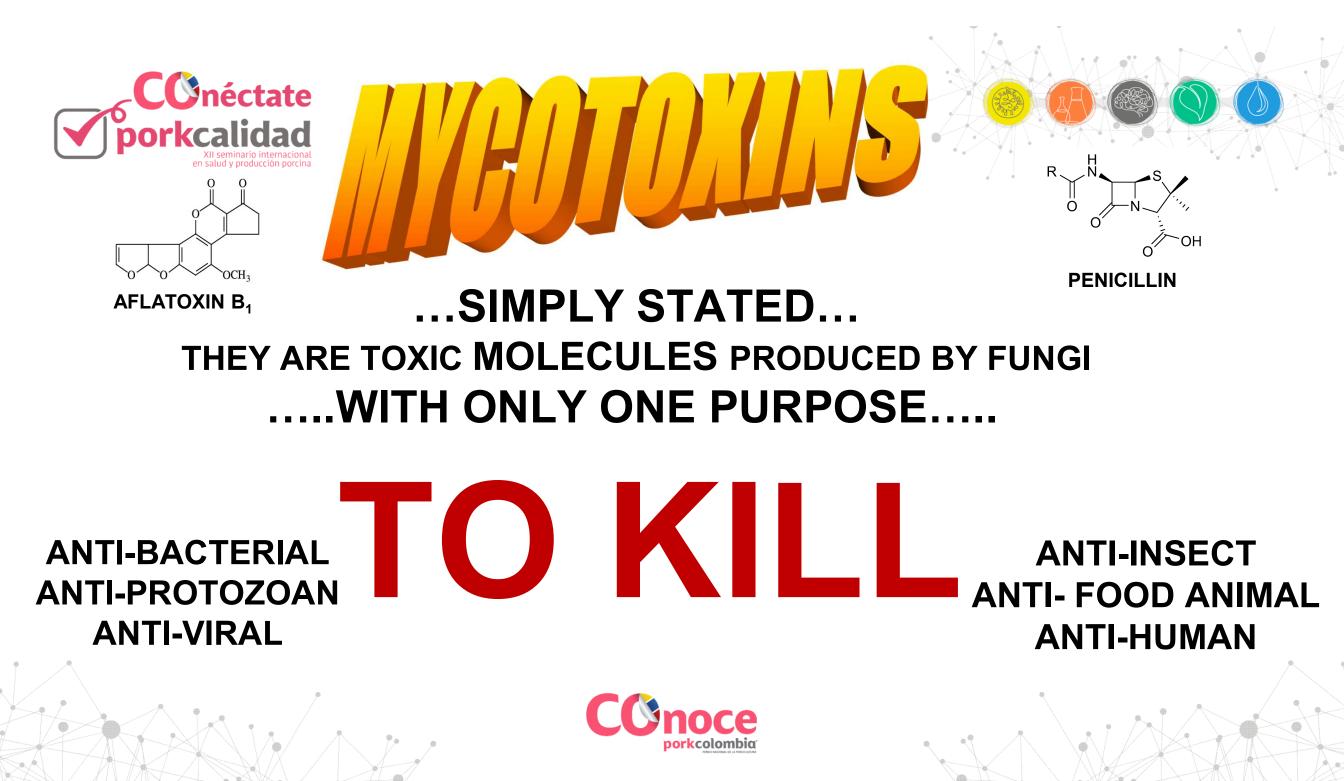


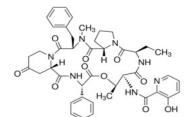


RICHARD D. MILES PROFESSOR EMERITUS UNIVERSITY OF FLORIDA









VIRGINIAMYCIN

#### ....SIMPLY STATED... THEY ARE TOXIC MOLECULES PRODUCED .....WITH ONLY ONE PURPOSE.....

OH

PENICILLIN

## TO KILL BACTERIA C©noce



## SIR ALEXANDER FLEMING

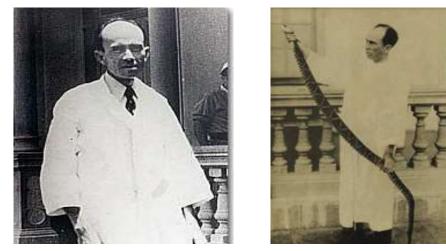
#### RECEIVED CREDIT FOR DISCOVERY OF PENICILLIN IN 1928 WHILE AT ST. MARY'S HOSPITAL IN LONDON, ENGLAND





## ...GIVING CREDIT WHERE CREDIT IS DUE...





#### **DR. CLODOMIRO PICADO TWIGHT**

DOCUMENTED THE DISCOVERY OF PENICILLIN IN HIS LABORATORY NOTEBOOKS (1915-1927) AND PUBLISHED HIS RESULTS IN 1927







## TWO MAJOR REASONS FOR THE USE OF ANTIBIOTICS IN ANIMALS





#### **GROWTH ENHANCEMENT/PROMOTION**

PROVIDED TO HEALTHY ANIMALS AT DIETARY CONCENTRATIONS OF BELOW 200 GRAMS PER TON OF FEED FOR MORE THAN 14 DAYS



Dr. Twight

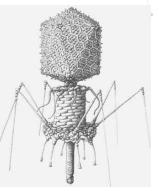
### **THERAPEUTIC AND PROPHYLACTIC USE**

**PROVIDED TO ANIMALS TO TREAT OR PREVENT INFECTION/DISEASE** 





## ...SIMPLY STATED... THEY ARE VIRAL ASSASSINS WITH ONLY TWO PURPOSES FOR THEIR EXISTENCE..... **TO KILL BACTERIA** AND REPLICATE Minoce





### WHEN WERE BACTERIOPHAGES DISCOVERED AND BY WHOM ?



## 1896 ERNEST HANKIN

ENGLISH BACTERIOLOGIST

FOR

e

FR.C.

QUESTION





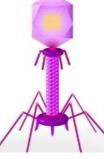
QUESTION

#### WHO DOCUMENTED THE ANTI-BACTERIAL NATURE OF PHAGES



### **1915** FREDERICK WILLIAM TWORT

#### **ENGLISH BACTERIOLOGIST**





#### ...HOWEVER... DID NOT KNOW THE MECHANISM OF BACTERIAL DESTRUCTION





QUESTION

WHO IS CREDITED WITH ISOLATING BACTERIOPHAGES AND DISCOVERING THAT BACTERIOPHAGES ARE RESPONSIBLE FOR KILLING BACTERIA ?

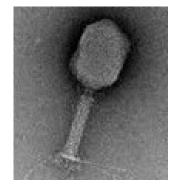


**1917** FELIX d' HERELLE FRENCH-CANADIAN MICROBIOLOGIST

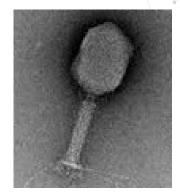
HE PROPOSED "PHAGE THERAPY" AND THE USE OF PHAGE COCKTAILS TO TREAT BACTERIAL DISEASES





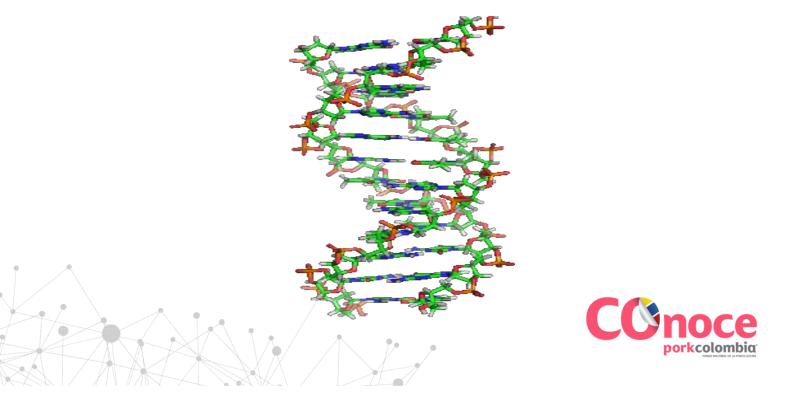


## BACTERIOPHAGE



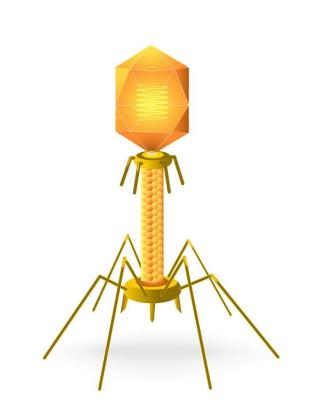
ARE THE MOST ABUNDANT/DIVERSE FORM OF DNA REPLICATING AGENT ON OUR PLANET

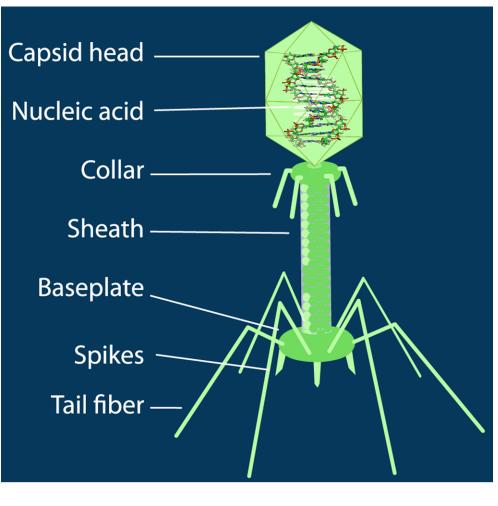
...FACTS...

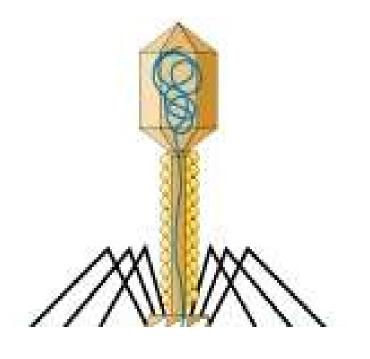




## **STRUCTURE**





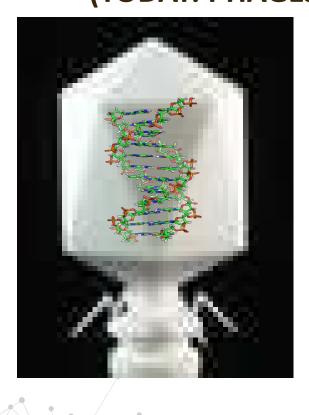








#### ARE THE MOST ABUNDANT/DIVERSE FORM OF DNA REPLICATING AGENT ON OUR PLANET (TODAY: PHAGES CAN BE NATURAL OR ENGINEERED)



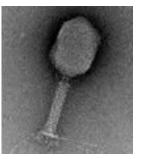
### HEADSIZE

~ 25-100 nm DEPENDING ON HOW MUCH DNA OR RNA IS PRESENT ...AND... THE GENOME MAY CONTAIN AS FEW AS 4 GENES OR SEVERAL HUNDRED GENES



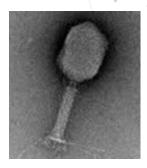






## **DO NOT MOVE INDEPENDENTLY**

#### (NO MEANS OF MOBILITY)



## DO NOT INFECT ANIMAL OR PLANT CELLS

#### (BACTERIA SPECIFIC)

## **DO NOT HAVE ANY ORGANELLS**

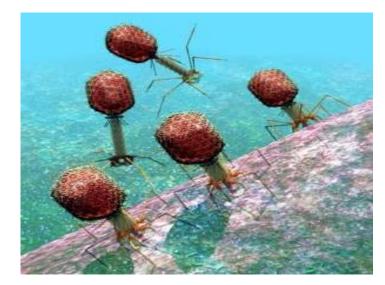
#### (NUCLEUS, RIBOSOMES, MITOCHONDRIA, ENDOPLASMIC RETICULUM, ETC.)

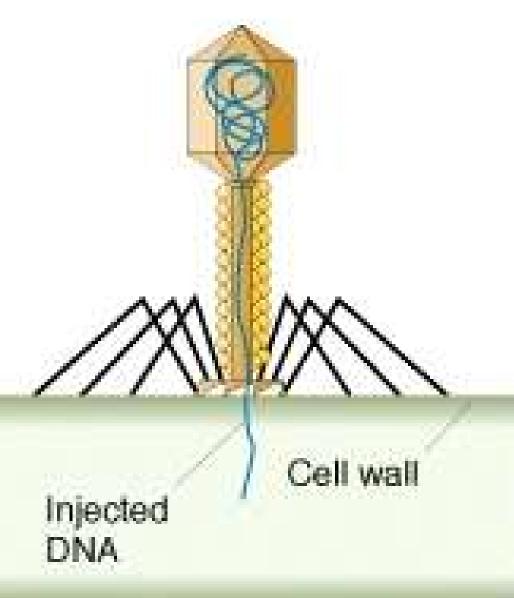
## DO NOT HAVE ANY METABOLIC PATHWAYS

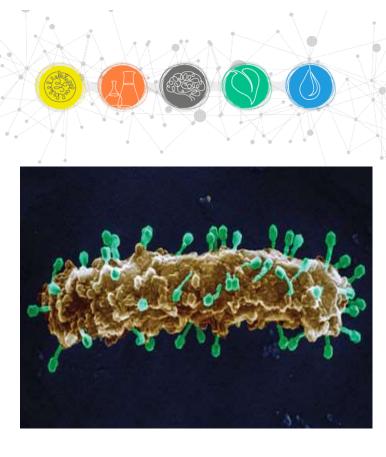
(THEREFORE, CANNOT METABOLIZE NUTRIENTS AND GENERATE ATP)











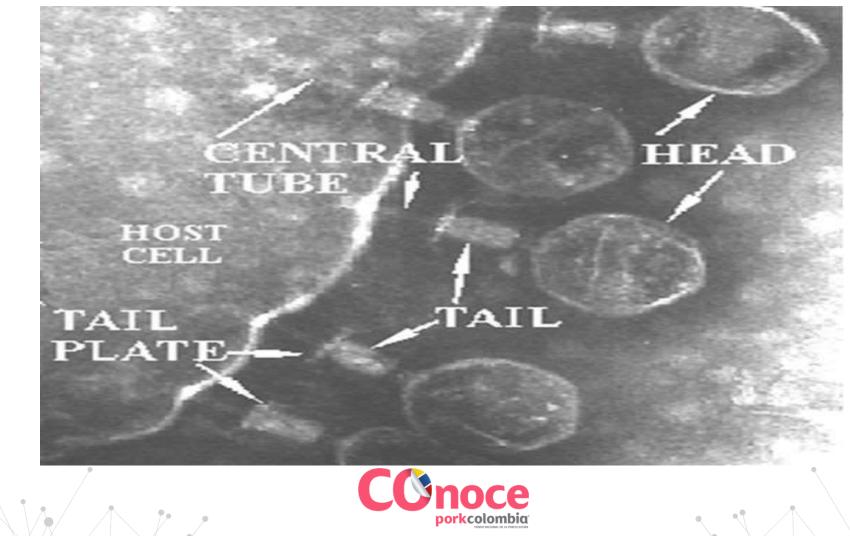






## BACTERIOPHAGE

**BINDING TO BACTERIA AND INJECTING DNA** 







## "LIFE CYCLE"

EXTRACELLULAR PHASE "INFECTIOUS VIRON"

#### INTRACELLULAR PHASE (LYTIC CYCLE OR LYSOGENIC CYCLE)

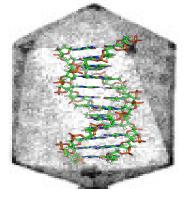




COnéctate 'LIFE CYCLE' **INTRACELLULAR PHASE** 

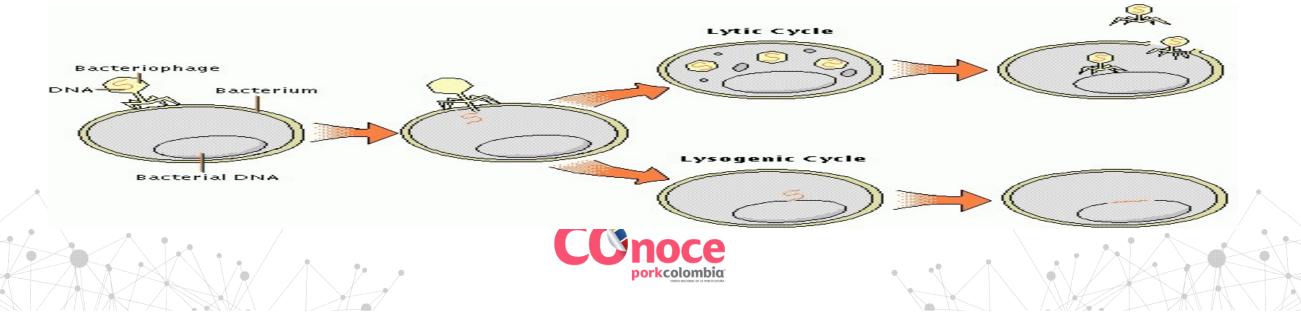


**GENETIC MATERIAL INJECTED INTO BACTERIA REPLICATED IN BACTERIA NEW PHAGES FORMED** BACTERIAL CELL BURSTS (LETHAL)



#### **YSOGENIC CYCLE**

**GENETIC MATERIAL INJECTED INTO BACTERIA** STORED IN BACTERIAL DNA **REMAINS DORMANT** (NON-LETHAL) (EVENTUALLY RELEASED/LYTIC CYCLE ACTIVATED)



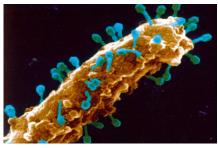


WHAT SEEMS TO CONTROL WHETHER A LYTIC CYCLE OR A LYSOGENIC CYCLE WILL OCCUR IN THE BACTERIA ?



#### CURRENT THINKING "BACTERIOPHAGE CONCENTRATION"





LOTS OF BACTERIA FEW PHAGES LYTIC CYCLE OCCURS LOTS OF PHAGES FEW BACTERIA LYSOGENIC CYCLE OCCURS

## QUESTION





QUESTION

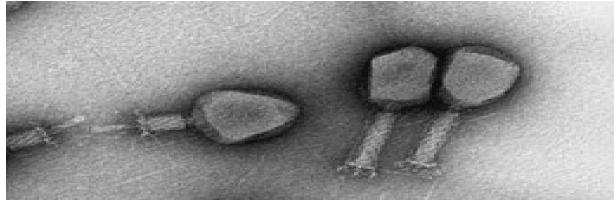
## WHERE CAN BACTERIOPHAGES BEFOUND ?

## BACTERIOPHAGES ARE UBIQUITOUS

## WHERE YOU FIND BACTERIA YOU WILL FIND BACTERIOPHAGES







(BACTERIAL SPECIES SPECIFIC) (NO BACTERIAL RESISTANCE DEVELOPS) (PROVIDE NON-HOST DERIVED IMMUNITY)



## ...FACT...



#### FOUND EVERYWHERE ON EARTH SEAWATER AND MICROBIAL MATS CONTAIN HIGH NUMBERS OF BACTERIOPHAGES (9 X 10<sup>8</sup>/ML)

#### IT IS ESTIMATED THAT BACTERIOPHAGES DESTROY UP TO 40% OF THE BACTERIA IN EARTH'S OCEANS DAILY



**O**néctate















HAVE BEEN USED FOR OVER 100 YEARS AS AN ALTERNATIVE TO ANTIBIOTICS IN THE FORMER SOVIET UNION, CENTRAL EUROPE AND FRANCE

**BACTERIOPHAGE BANKS/LIBRARIES EXIST** 



BACTERIOPHAGE THERAPY IS AVAILABLE TO TREAT INFECTIOUS DISEASES CONSIDERED UNTREATABLE ("PHAGE THERAPY CENTERS EXIST)

CONTROL BACTERIAL ECOSYSTEMS EVERYWHERE (ESPECIALLY IN AN ANIMAL'S DIGESTIVE TRACT)







### EARLY "BACTERIAL STABILITY" IS IMPORTANT IN AN ANIMAL'S DIGESTIVE TRACT



## BACTERIAL INFECTION RISK "HIGH" IMMUNE SYSTEM "NOT FULLY DEVELOPED"









WHAT IS A MAJOR WAY THAT BACTERIOPHAGES PROTECT THE ANIMAL'S DIGESTIVE TRACT



#### PATHOGENS ENTER THROUGH MUCOSAL SURFACES MUCUS MAINTAINS A HIGH PHAGE TO BACTERIA RATIO WHICH PROTECTS THE UNDERLYING EPITHELIUM AND PREVENTS INFECTION

THE BACTERIOPHAGE BINDS TO THE MUCIN GLYCOPROTEINS AND ATTACHMENT TO THE MUCIN RESULTS WHICH PROVIDES A "NON-HOST DERIVED IMMUNITY" BY DECREASING BACTERIAL NUMBERS



QUESTION







#### BACTERIOPHAGES ASSOCIATE TIGHTLY WITH MUCIN "VELCRO EFFECT"





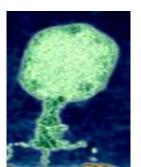




#### **COnéctate BACTERIOPHAGES** ...PROMOTE...

#### **HEALTH OF THE DIGESTIVE TRACT AND A STABLE MICROBIAL POPULATION**





# "PHAGEBIOTI





DO BACTERIOPHAGES ENTER THE BODY OF THE ANIMAL FROM THE LUMEN OF THE INTESTINAL TRACT?



THEY ENTER THE BLOODSTREAM FROM THE INTESTINE AND OTHER REGIONS OF THE BODY AND TRANSPORTED ALL OVER THE BODY TO VARIOUS ORGANS AND TISSUES

...<u>THIS IS KNOWN AS</u>...

"PHYSIOLOGICAL VIREMIA" AND "VIRAL TRANSLOCATION"



QUESTION

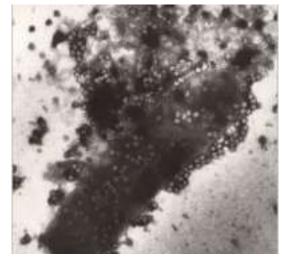


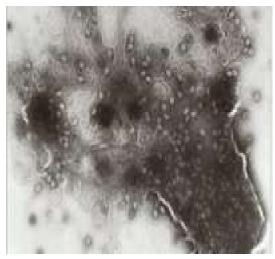
QUESTION

WHEN ONE BACTERIOPHAGE INJECTS ITS DNA INTO A BACTERIAL CELL AND CELL LYSIS OCCURS HOW MANY NEW BACTERIOPHAGES CAN BE FORMED ONCE "BURST SIZE" IS REACHED ?



### THE NUMBER CAN VARY BUT FROM 50-100(200) IS COMMON



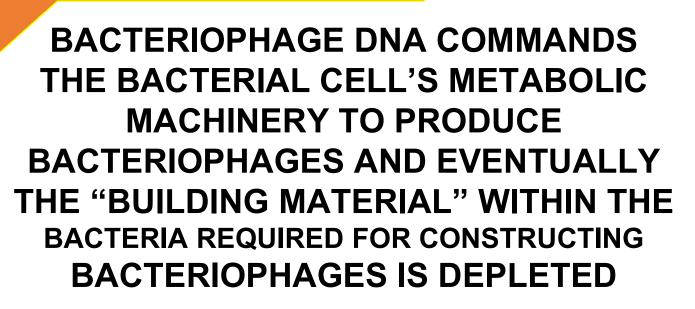


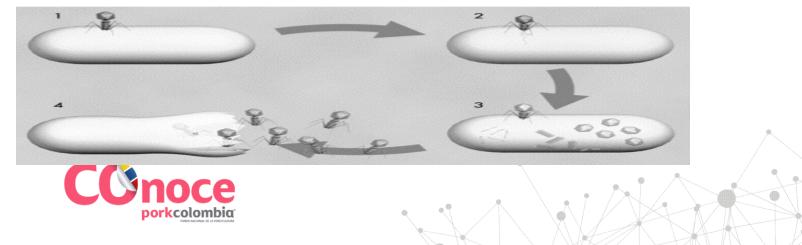
**BACTERIAL CELL LYSIS** 





WHAT LIMITS THE NUMBER OF NEW BACTERIOPHAGES ? WHY NOT MORE, LET'S SAY 300, 500, 1000, 5,000 +





QUESTION

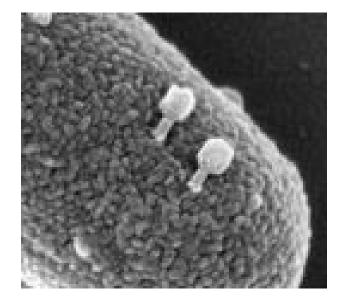


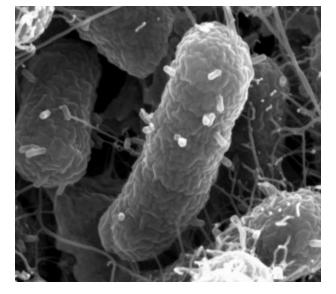
QUESTION

#### IN COMPARISON TO BACTERIA HOW BIG ARE BACTERIOPHAGES ?



#### BACTERIOPHAGES ARE NORMALLY ABOUT 100 TIMES SMALLER THAN BACTERIA





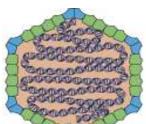




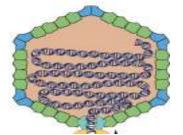
WHAT HAPPENS TO THE BACTERIOPHAGE IN THE ENVIRONMENT AFTER ITS DNA HAS BEEN INJECTED INTO THE BACTERIA ?



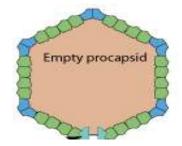
#### THE BACTERIOPHAGE IS THEN NOTHING BUT AN EMPTY PROTEIN SHELL WHICH WILL EVENTUALLY DECAY











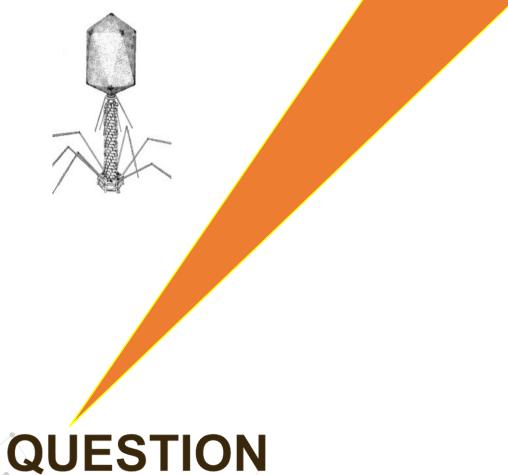


QUESTION

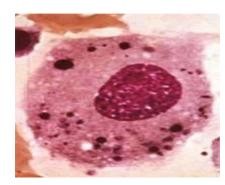


WHAT HAPPENS TO THE BACTERIOPHAGE IN THE ANIMAL AFTER ITS DNA HAS BEEN INJECTED INTO THE BACTERIA ?









RETICULOENDOTHELIAL SYSTEM "MACROPHAGE SYSTEM"

## IN THE ANIMAL

THE MACROPHAGES CONSUME THE EMPTY SHELL OF THE BACTERIOPHAGES





QUESTION

### DO BACTERIOPHAGE RESISTANT BACTERIA EVER DEVELOP ?



THE RESISTANT BACTERIA ARE A MINORITY AND THE BACTERIOPHAGES ARE CONSTANTLY CO-EVOLVING AND WILL EVENTUALLY DESTROY THE BACTERIA

...HOWEVER...

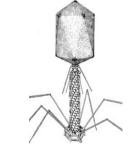
## **3.5 BILLION YEARS WITHOUT ANY TOTAL RESISTANCE DEVELOPING**







DEVELOPING RESISTANCE TO BACTERIOPHAGES IS NOT WITHOUT CONSEQUENCES AND IS COSTLY TO THE BACTERIA



## ...BACTERIA EXHIBIT...

- 1) LESS VIRULENCE TO HOST
- 2) LOWER REPLICATION RATE
- 3) DECREASED LIFE SPAN
- 4) INCREASED SENSITIVITY TO ANTIBIOTICS
- 5) INABILITY TO ATTACH TO AND INVADE HOST CELLS

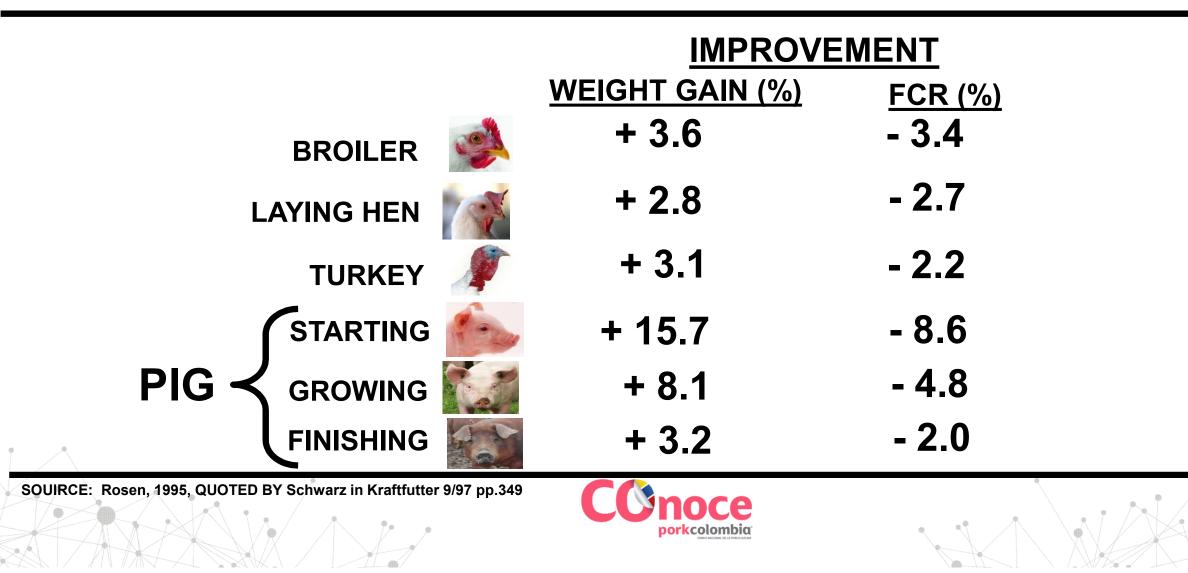




## GROWTH PROMOTING ANTIBIOTICS



#### "EXPECTED PERFORMANCE RESPONSES"







#### **MAJOR FACTORS** KNOWN TO INFLUENCE THE MAGNITUDE OF RESPONSE TO GROWTH PROMOTING ANTIBIOTICS IN VARIOUS SPECIES OF ANIMALS

## **FACTOR**



**GERM FREE ENVIRONMENT (NO MICROBES)** 

FARM HYGIENE (CLEAN VS DIRTY)



AGE OF ANIMAL (YOUNG VS OLD)

FARM MANAGEMENT (STRESS LEVEL)





**GERM FREE ENVIRONMENT (NO MICROBES)** 

FARM HYGIENE (CLEAN VS DIRTY)

AGE OF ANIMAL (YOUNG VS OLD)

FARM MANAGEMENT (STRESS LEVEL)

RESPONSE IN ANIMAL PERFORMANCE











#### **GERM FREE ENVIRONMENT (NO MICROBES)**



#### THIS IS ALSO TRUE WHEN USING BACTERIOPHAGES

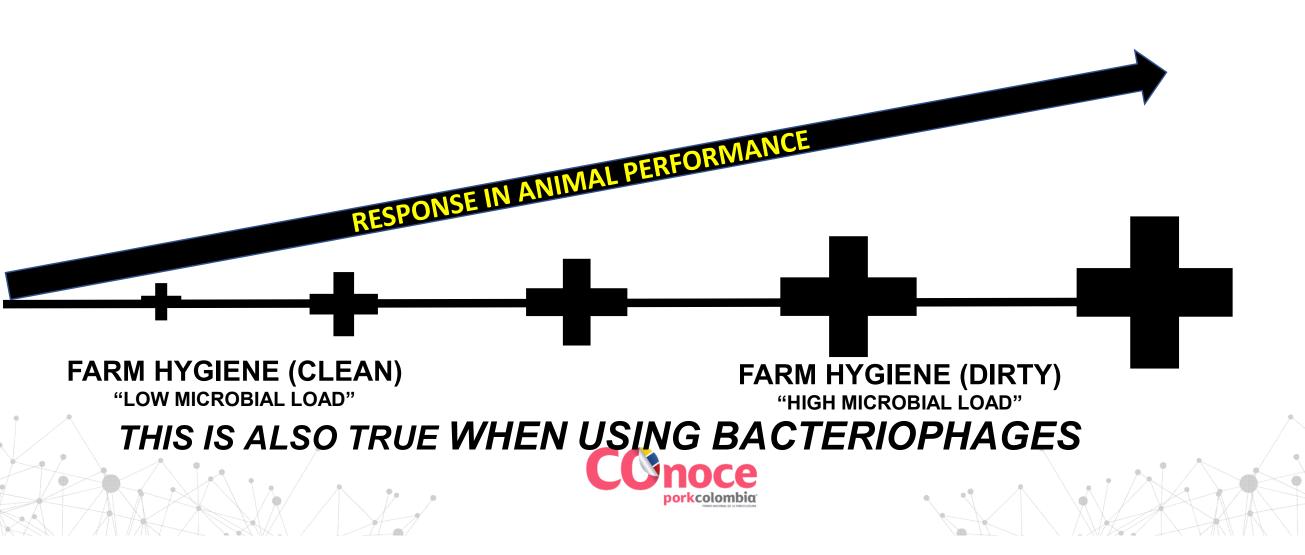
RESPONSE IN ANIMAL PERFORMANCE







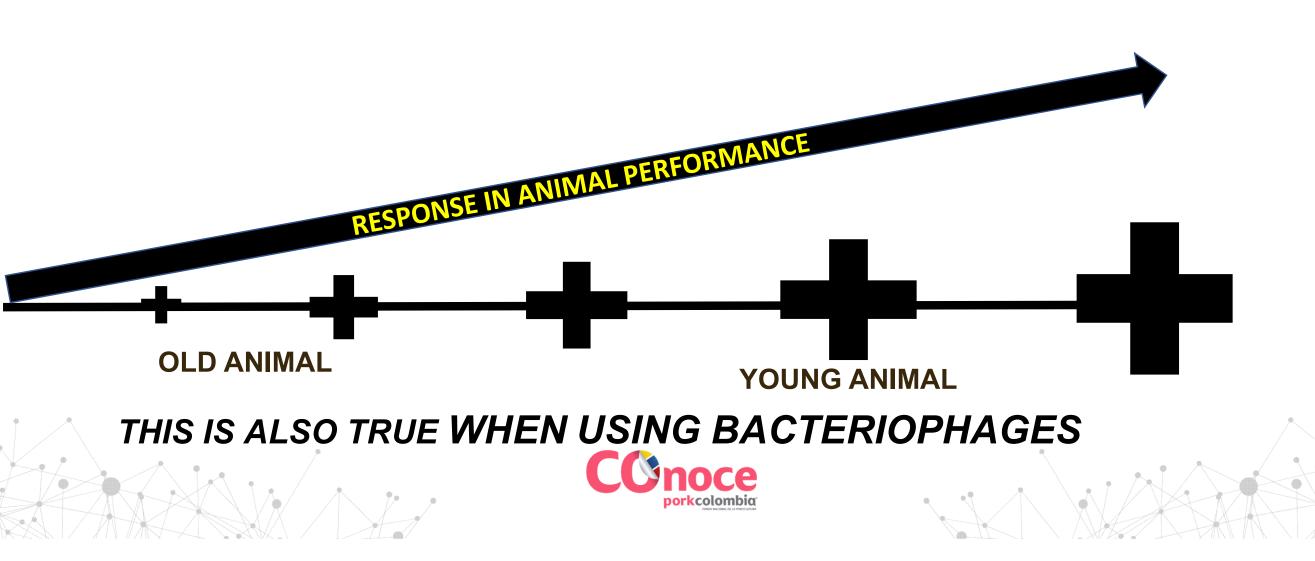
#### FARM HYGIENE (CLEAN VS DIRTY)







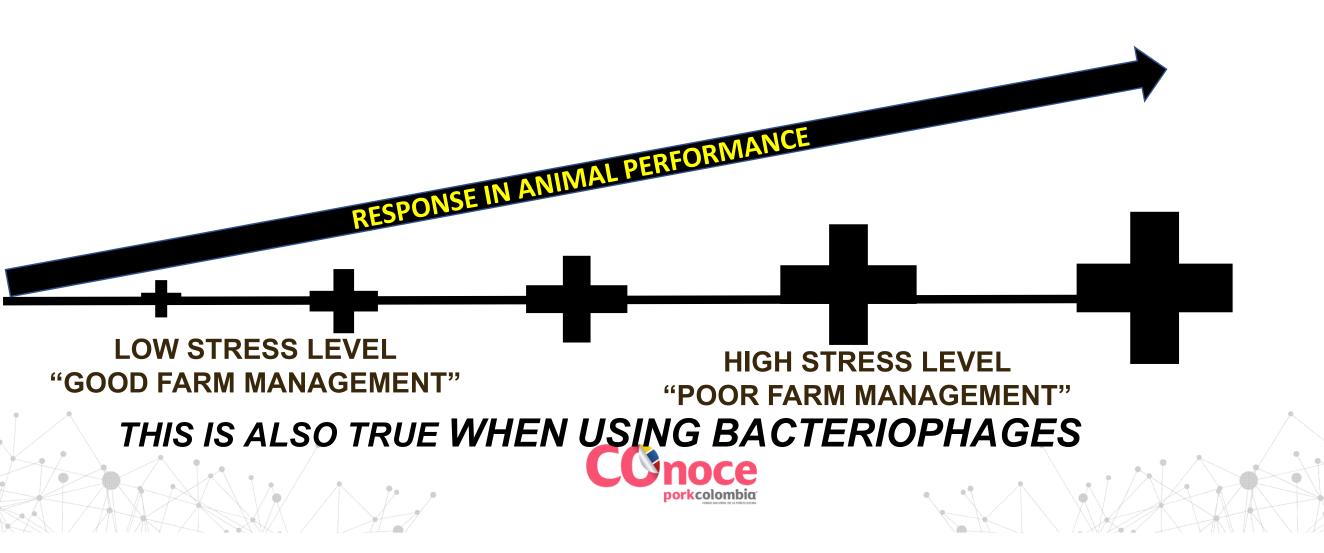
#### AGE OF ANIMAL (YOUNG VS OLD)







#### FARM MANAGEMENT (STRESS LEVEL)











#### CONSUMER DEMAND HAS ALWAYS BEEN THE MAJOR DRIVING FORCE IN THE ANIMAL MEAT INDUSTRY ...AND NOW...

CONSUMERS ARE DEMANDING ALL ANIMAL PRODUCTS BE PRODUCED WITHOUT THE USE OF ANTIBIOTICS

EUROPEAN UNION: 1/1/2006

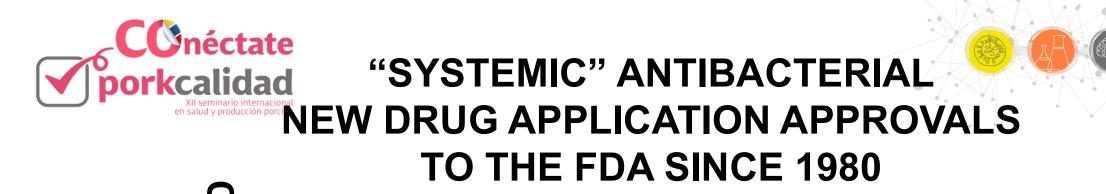




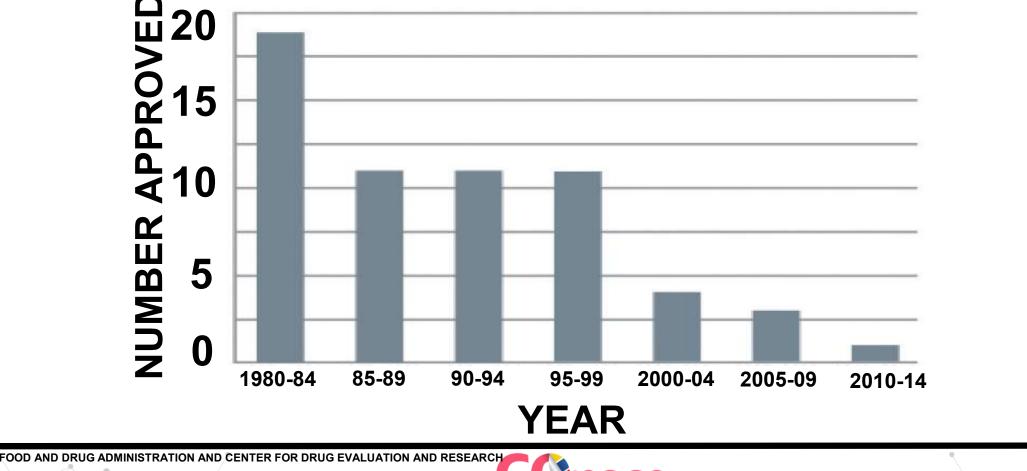


#### THE COST OF DEVELOPMENT AND TESTING ANTIBIOTICS IS BECOMING COST PROHIBITIVE AND THE FUTURE TREND SEEMS TO BE NOT TO APPROVE AS MANY NEW ANTIBIOTICS AS IN THE PAST



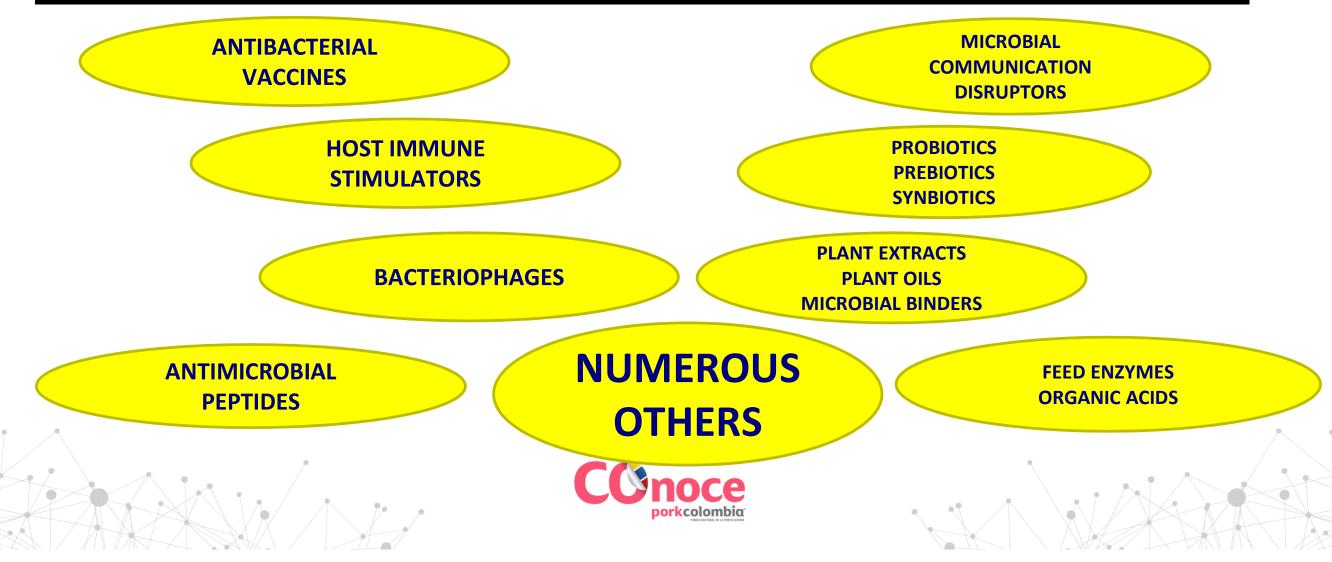


SOURCE: THE I



COnoce

#### COnéctate POSSIBLE orkcalidad ALTERNATIVE REPLACEMENTS FOR GROWTH PROMOTING ANTIBIOTICS



### CCnéctate orkcalidad GROWTH PROMOTING ANTIBIOTIC ALTERNATIVES





QUESTION

## CAN BACTERIOPHAGES BE USED WITH ANTIBIOTICS ?



# YES... VERY SUCCESSFULLY

## **ANTIBIOTICS**

ARE NOT SPECIFIC FOR A CERTAIN BACTERIAL SPECIES AND EVEN LESS SPECIFIC AGAINST CERTAIN STRAINS OF BACTERIA WITHIN A SPECIES

(USUALLY KILL BACTERIA UNDERGOING A RAPID GROWTH PHASE)

## **BACTERIOPHAGES**

ARE VERY SPECIFIC FOR ONLY ONE BACTERIAL SPECIES AND SPECIFIC FOR CERTAIN STRAINS WITHIN A SPECIES (KILL BACTERIA INDEPENDENTLY OF THE GROWTH PHASE)





## **HOW SAFE ARE BACTERIOPHAGES** ???? **VERY SAFE APPROVED BY USDA, FDA & FSIS** FOR USE ON MANY FOOD ITEMS

(SUCH AS CARCASSES AND READY TO EAT MEAT PRODUCTS)

















## ...BACTERIOPHAGES.

FAVORABLE EXPECTED CONSEQUENCES OF THEIR USE IN ANIMAL DIETS

GROWTH ENHANCEMENT IMPROVED FEED CONVERSION IMPROVED FLOCK/HERD UNIFORMITY LESS SUBCLINICAL DISEASE BETTER INTESTINAL "BACTERIAL STABILITY" (PREVENT DYSBACTERIOSIS) REDUCED IMMUNE STIMULATION IMPROVED PRODUCT SAFETY & QUALITY



**OTHERS** 



**Néctate** ANTIBIOTICS.

## THIS HEADLINE SUMS UP EVERYTHING ABOUT THE FUTURE USE OF ANTIBIOTICS USED FOR GROWTH PROMOTION



# Science & the Public

Humans & Society, Nutrition, Earth & Environment Biomedicine, Agriculture

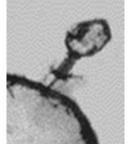
Growth-promoting antibiotics: On the way out?

Court instructs r DA to resume efforts aimed at barming use of low-dose antibiotics in livestock feed

By Janet Raloff 1:30pm, March 23, 2012







# ...IN THE PAST AND PRESENTLY... MOST BACTERIOPHAGE RESEARCH IS RELATED TO HUMANS

PIL ES



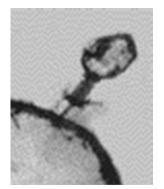
## "PHAGE THERAPY"



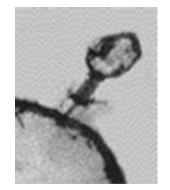








# RECENT RESEARCH INTEREST IN THE USE OF BACTERIOPHAGES IN ANIMAL DIETS IS INCREASING AT A VERY RAPID RATE AND



INTEREST WILL CONTINUE TO INCREASE AS WE DISCOVER MORE ABOUT THERE BENEFITS IN PROMOTING ANIMAL PERFORMANCE





## **PUBLISHED RESEARCH**



Effects of Dietary Supplementation of Bacteriophage on Productive Performance and Egg Quality in Laying Hens after Forced-molting G. P. Han, J. E. Shin, J. H. Kim, and D. Y. Kil Department of Animal Science and Technology, Chung-Ang University, Anseoralisi, Republic of Korea











Bacteriopha bacteriophage

Evaluation of ba

digestibility, blood charad

characteristics

Effect of bag

AJAS, 2012





# **PUBLISHED RESEARCH**

- Effect of dietary supplementation of bacteriophage on performance, egg quality and caecal bacterial populations in laying hens. British Poultry Science, 2015
- Effect of dietary supplementation of bacteriophage cecal bacterial populations in broiler chick Livestock Science 2014

h performance and erent housing systems.

e of growing pigs but

formance, blood oners. AJAS, 2013

STORIES with performance, nutrient necal microbial shedding in growing pigs.

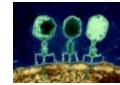
Effective of bacteriophage supplementation on egg performance, egg quality, excreta microflora, and moisture content in laying hens. AJAS, 2012





# **PUBLISHED RESEARCH**

PERMPIE ES









- Bacteriophage based nature friendly control technology for prevention and treatment of bacterial infection commonly encountered in flounder
   Paralichthysolivaceus culture. 5th Int. Symposium Care Aquaculture. Asia, 2015
- Protective ef weaned pir
  Protective ef weaned pir
- Effect of dietary supplementation of bacteriophage on laying performance, egg quality, and cecal microbial population in laying hens. WCAP, 2013











## **PUBLISHED RESEARCH**



Occurrence of *Salmonella*-Specific Bacteriophages in Swine Feces Collected from Commercial Farms

Todd R. Callaway,<sup>1</sup> Tom S. Edrington,<sup>1</sup> Andrew Brabban,<sup>2</sup> Elizabeth Kutter,<sup>2</sup> Locke Karriker,<sup>3</sup> Chad Stahl,<sup>4</sup> Elizabeth Wagstrom,<sup>5</sup> Robin C. Anderson Ken Genovese,<sup>1</sup> Jack McReynolds,<sup>1</sup> Roger Harvey,<sup>1</sup> and David J. Nisbet<sup>1</sup>









The Efficacy of Isolated Bacteriophages from Pig Farms against ESBL/AmpC-Producing *Escherichia coli* from Pig and Turkey Farms







READPLICES.





#### Phage Therapy To Reduce Preprocessing Salmonella Infections in Market-Weight Swine

Samantha K. Wall, Jiayi Zhang, Marcos H. Rostagno, Paul D. Ebner







Bacteriophages as an microbial agents against major pathogens in swine: a review

Jiancheng Zhang, Zhen Li, Zhenhui Cao, Lili Wang, Xiaoyu Li, Shuying Li, and Yongping Xu<sup>X</sup>









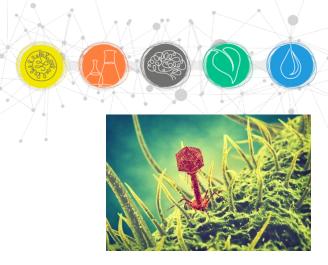
## **PUBLISHED RESEARCH**











## **INFINALLY...** HOW DO I FEEL ABOUT THE FUTURE WITHOUT ANTIBIOTICS











