Benefits of Microbiome Manipulation in Reducing Antibiotic Resistance

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Disclosures

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- Advisory Boards: None
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  - National Institutes for Health
  - Veterans Affairs Research and Development

Acknowledgments

- Erik R. Dubberke, MD, MSPH

- Steve Eppes, MD

- Erik VonRosenvinge, MD

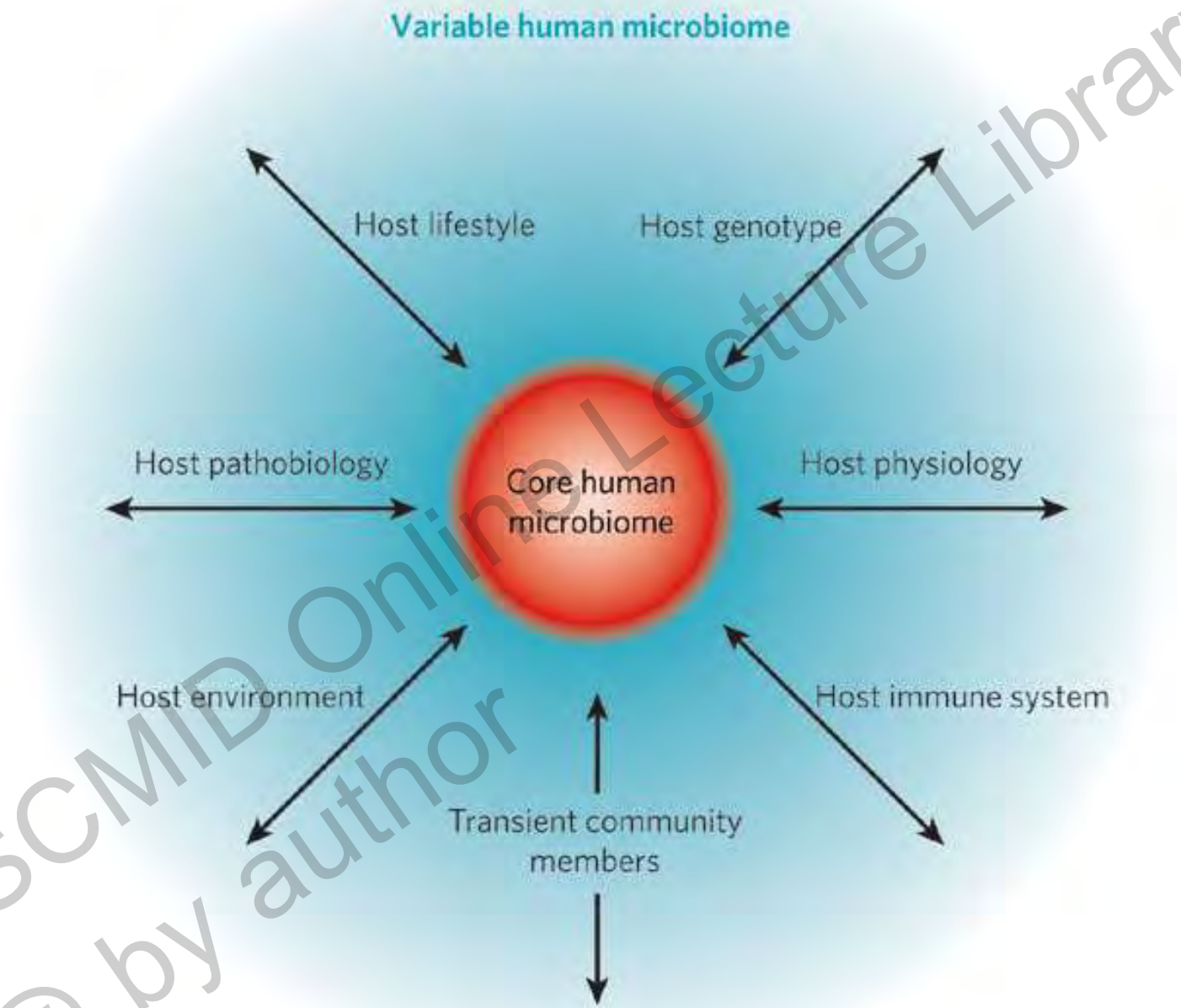
REPORT TO THE PRESIDENT ON COMBATING ANTIBIOTIC RESISTANCE

- Human Health Care
- Animal Agriculture
- Surveillance and Response
- Drug Development

Human Microbiome

- Human body = human cells + **microbial cells**
  - 1:10 ratio
- Human genetic landscape = Σ (human genome + **microbiome**)
  - 1:100 ratio
- Human metabolic features = human and **microbial** attributes

NIH HUMAN MICROBIOME PROJECT



The Human Microbiome Project. Peter J. Turnbaugh, Ruth E. Ley, Micah Hamady, Claire M. Fraser-Liggett, Rob Knight & Jeffrey I. Gordon Nature 449, 804-810(18 October 2007)

What the Human Microbiome does for us

Maintaining Health

- Harvest of otherwise inaccessible nutrients and sources of energy from our diet
- Drug metabolism and bioavailability
- Development our immune system

Cause Disease?

- Metabolic
  - Obesity / Metabolic syndrome
  - Type II diabetes
- Gastrointestinal
  - Irritable bowel syndrome
  - Colorectal cancer
- Neurologic
  - Autism
  - Multiple sclerosis
- Immunologic
  - Rheumatoid arthritis
  - Sclerosing cholangitis

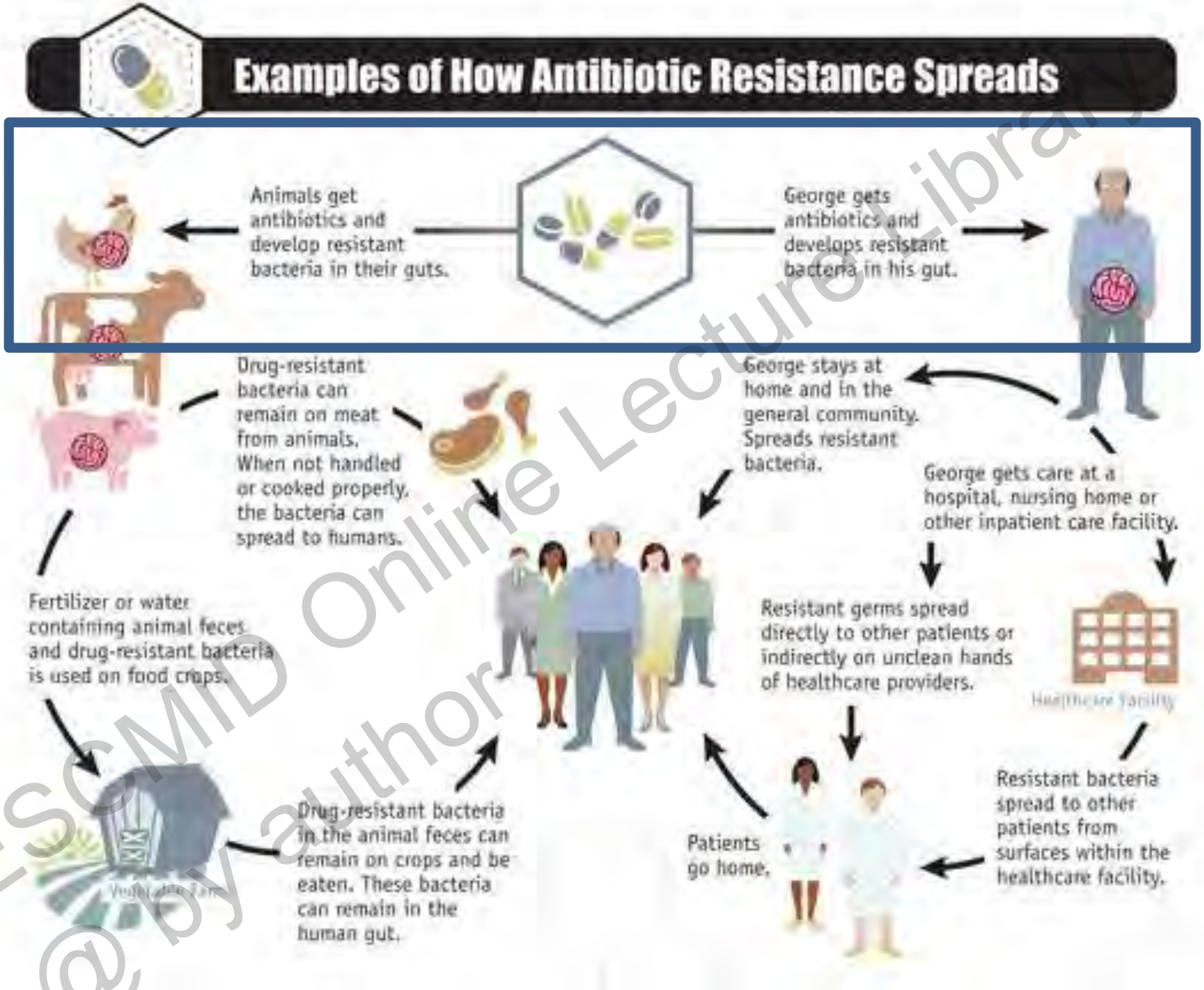
Turnbaugh, Nature, 2007

Human Health and our Microbiome

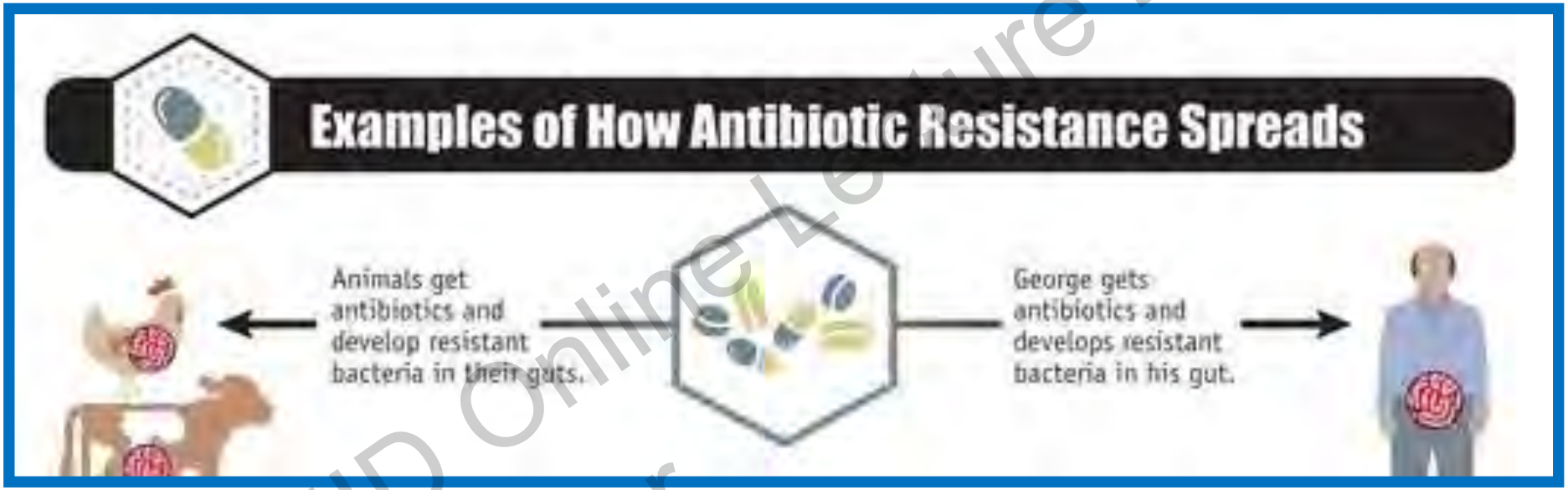
- Manipulation of the microbiota composition through
  - Anti-biotics: kills groups of bacteria
  - Pro-biotics: adds “beneficial” bacteria
  - Pre-biotics: selectively supports “beneficial” bacteria
- could be a novel therapeutic approach for diseases caused by disturbances in our microbiome.

Antibiotic Resistance and our Microbiome

- Manipulation of the microbiota composition through
  - Pro-biotics: adds “beneficial” bacteria
  - Pre-biotics: selectively supports “beneficial” bacteria
- could be a novel therapeutic approach for preventing antibiotic resistance.



David Wallinga, MD Huffington Post



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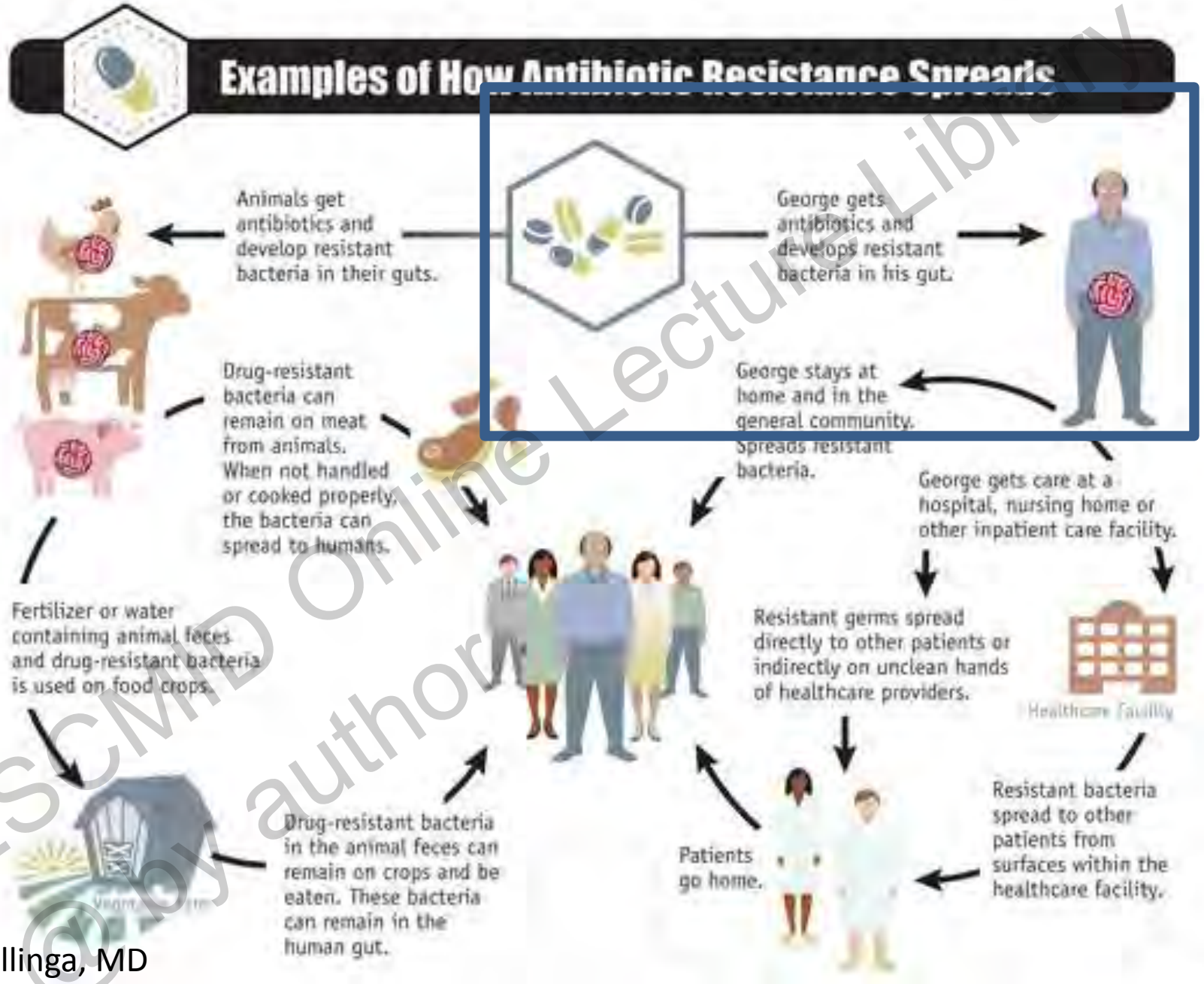

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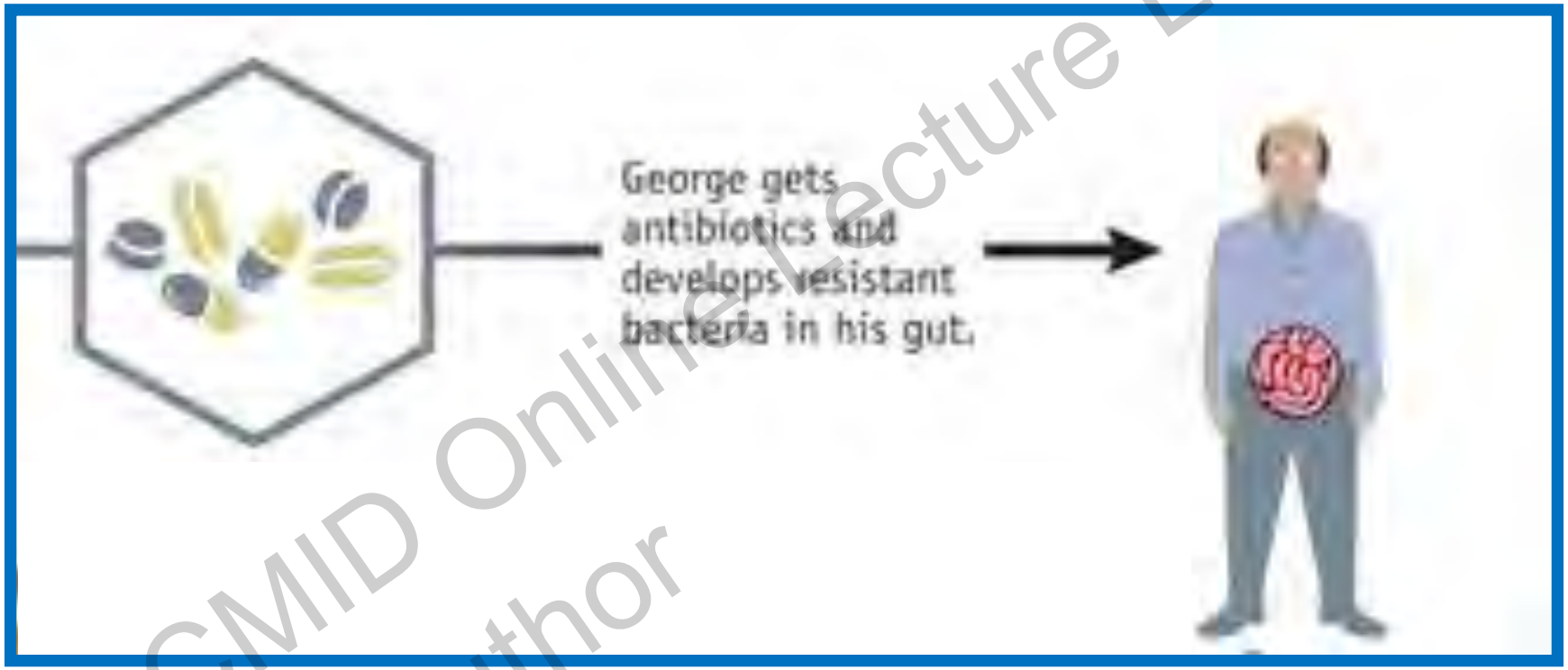

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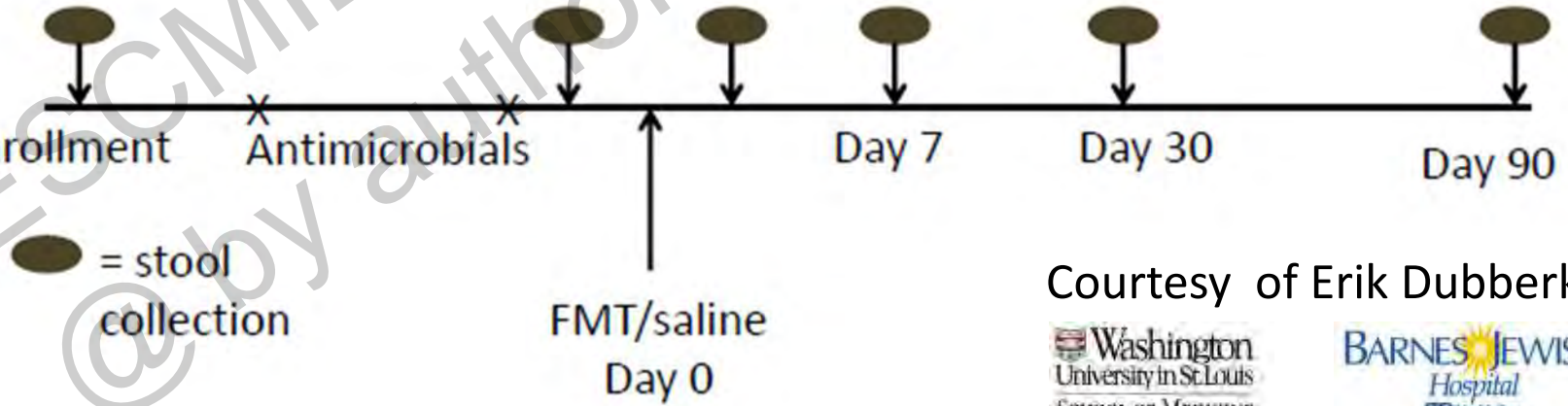
Autologous Fecal Microbiota Therapy

- Collect stool from 10 healthy volunteers
- Give five days of amoxicillin/clavulanic acid
- Give an enema of the collected fecal filtrate or normal saline
- Assess changes in the fecal microbiome in response to antibiotic therapy and then the fecal microbiota therapy

Analysis Underway



Courtesy of Erik Dubberke

Washington University in St. Louis School of Medicine

Barnes-Jewish Hospital BJC HealthCare

REPORT TO THE PRESIDENT ON COMBATING ANTIBIOTIC RESISTANCE

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  - Auto transplant post antibiotics
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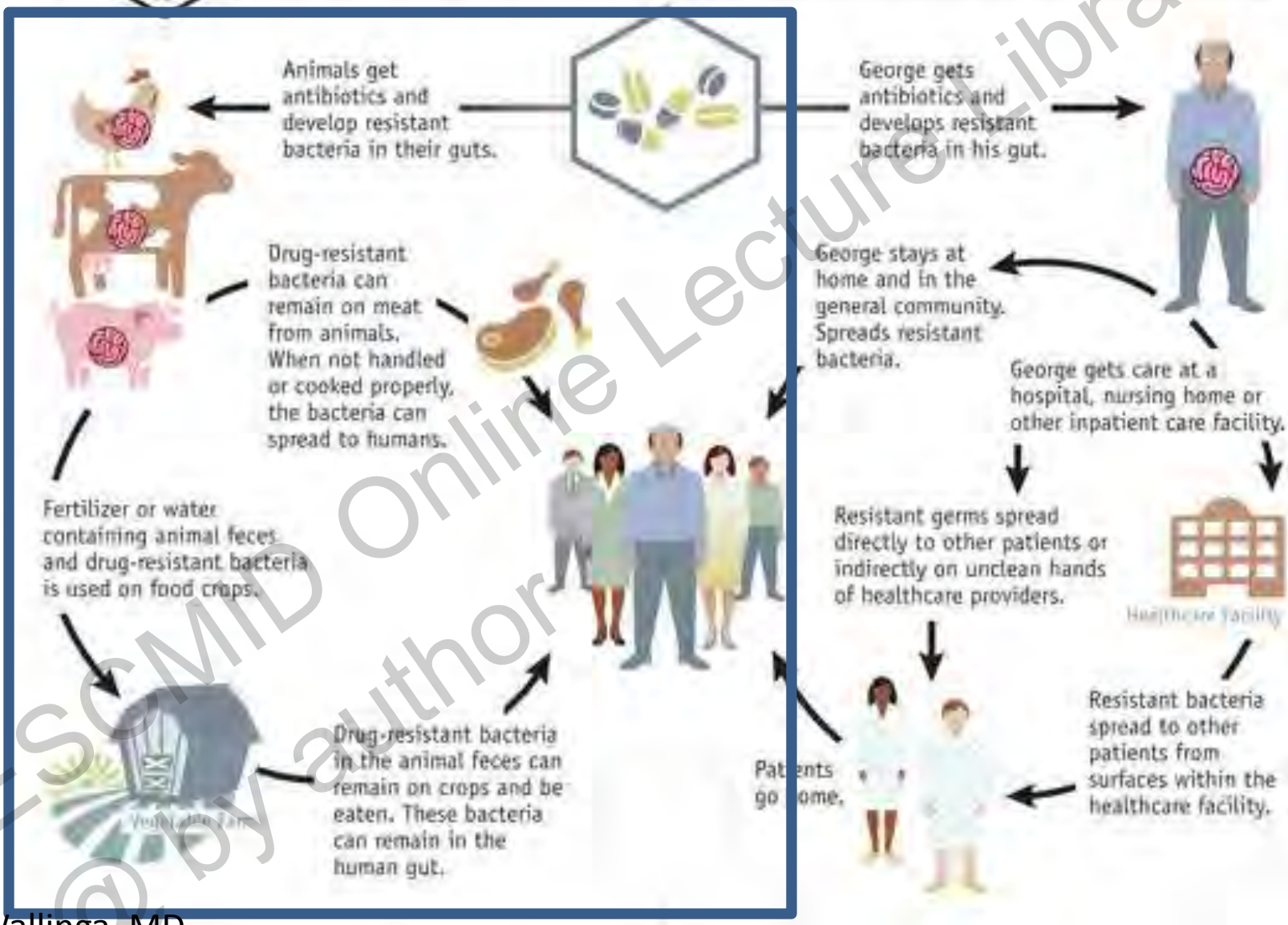
Examples of How Antibiotic Resistance Spreads



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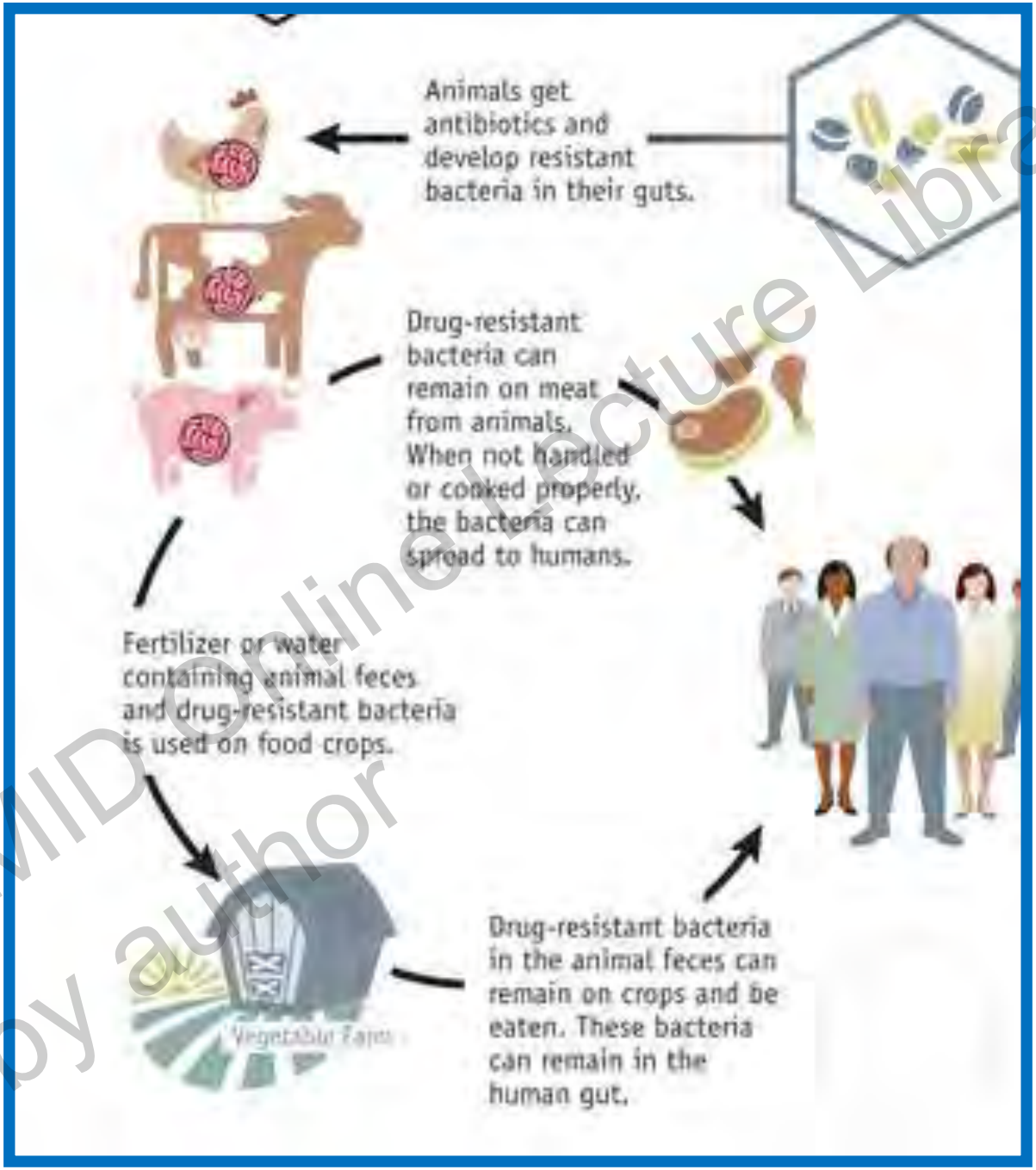

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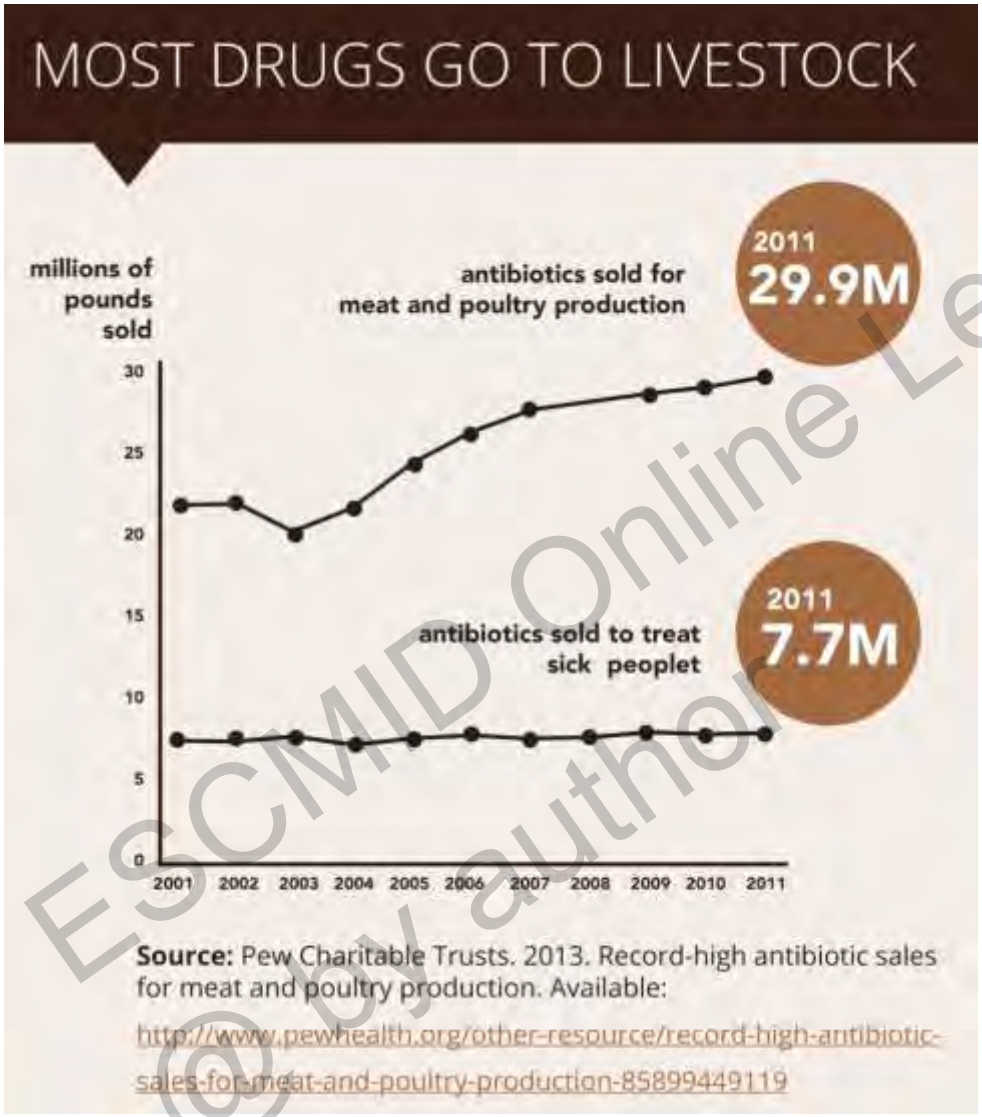
Antibiotic Use in Livestock



Why?

- Gain more body weight
- Treatment or prevention of disease
- Live longer
- Shelf life of products extended

PoultryStar®

EU REGISTERED

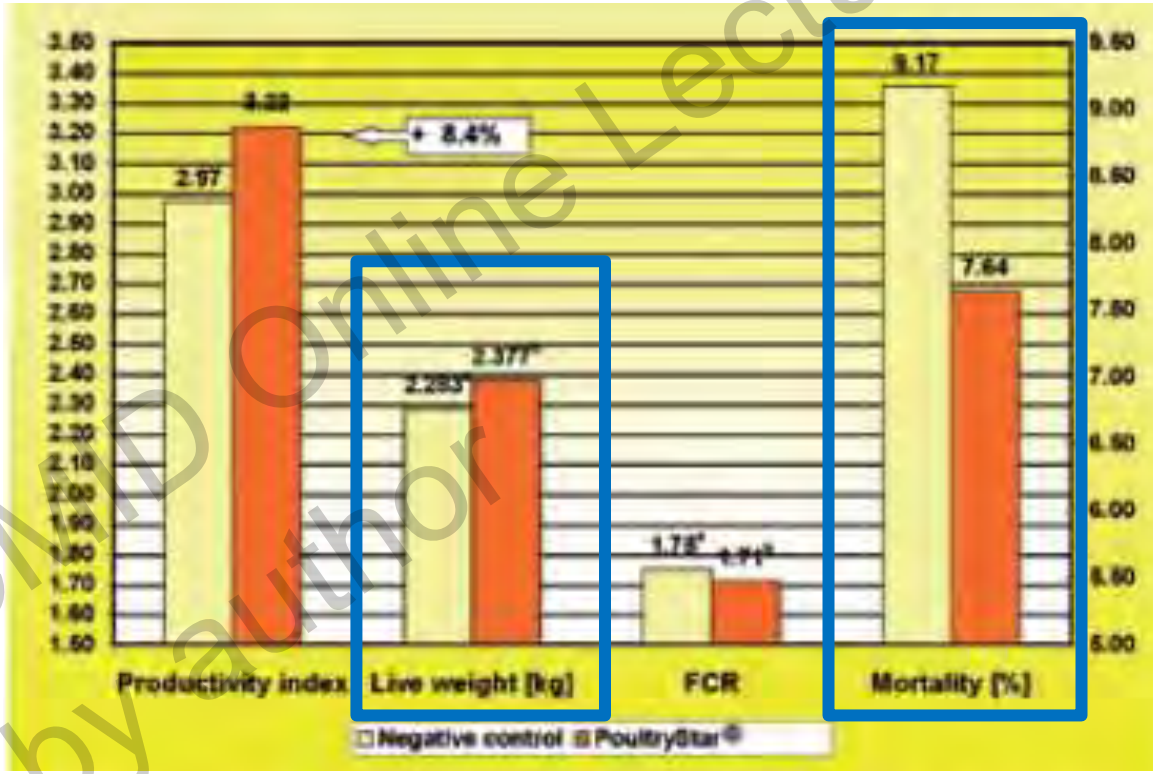
Healthy gut – strong chick!

- Probiotic strains
  - derived from healthy chickens
- Prebiotic fructoologosaccharides
  - stimulate growth of Bifidobacterium in large intestine
- Adhesion capability to intestinal cell lines
- Inhibition of pathogens
  - Salmonella
  - Campylobacter
- Immunologic activity

PoultryStar®

EU REGISTERED

Healthy gut – strong chick!



http://www.thepoultrysite.com/focus/biomin/2270/biomin-poultrystar-defined-probiotic-product-proves-efficacy

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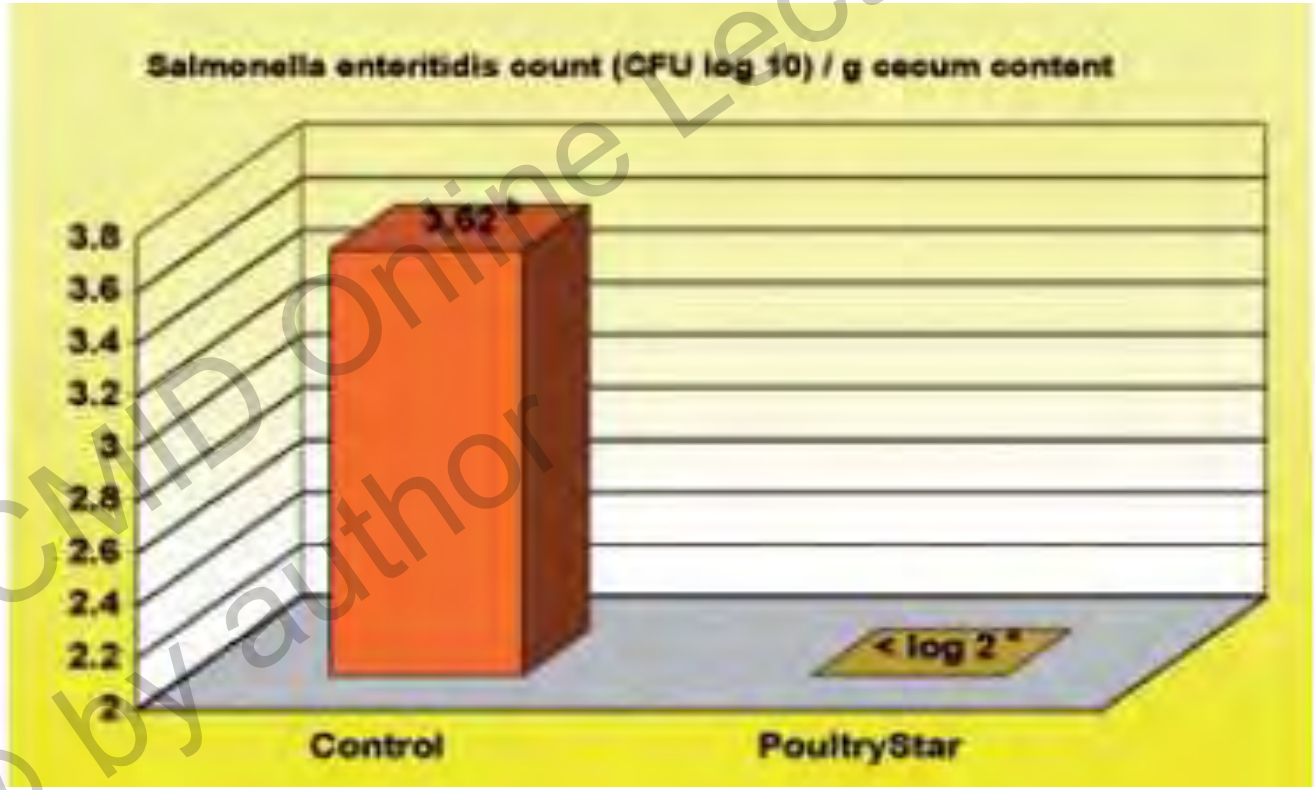

http://www.thepoultrysite.com/focus/biomin/2270/biomin-poultrystar-defined-probiotic-product-proves-efficacy

Giving Chickens Bacteria … To Keep Them Antibiotic-Free

- Probiotics such as Enterococccci, Lactobaccili and Bifidobacteria in the feed promote growth and prevent disease

THE SALT

Perdue Says Its Hatching Chicks Are Off Antibiotics

- Vegetarian diet
- Vaccination

npr the salt

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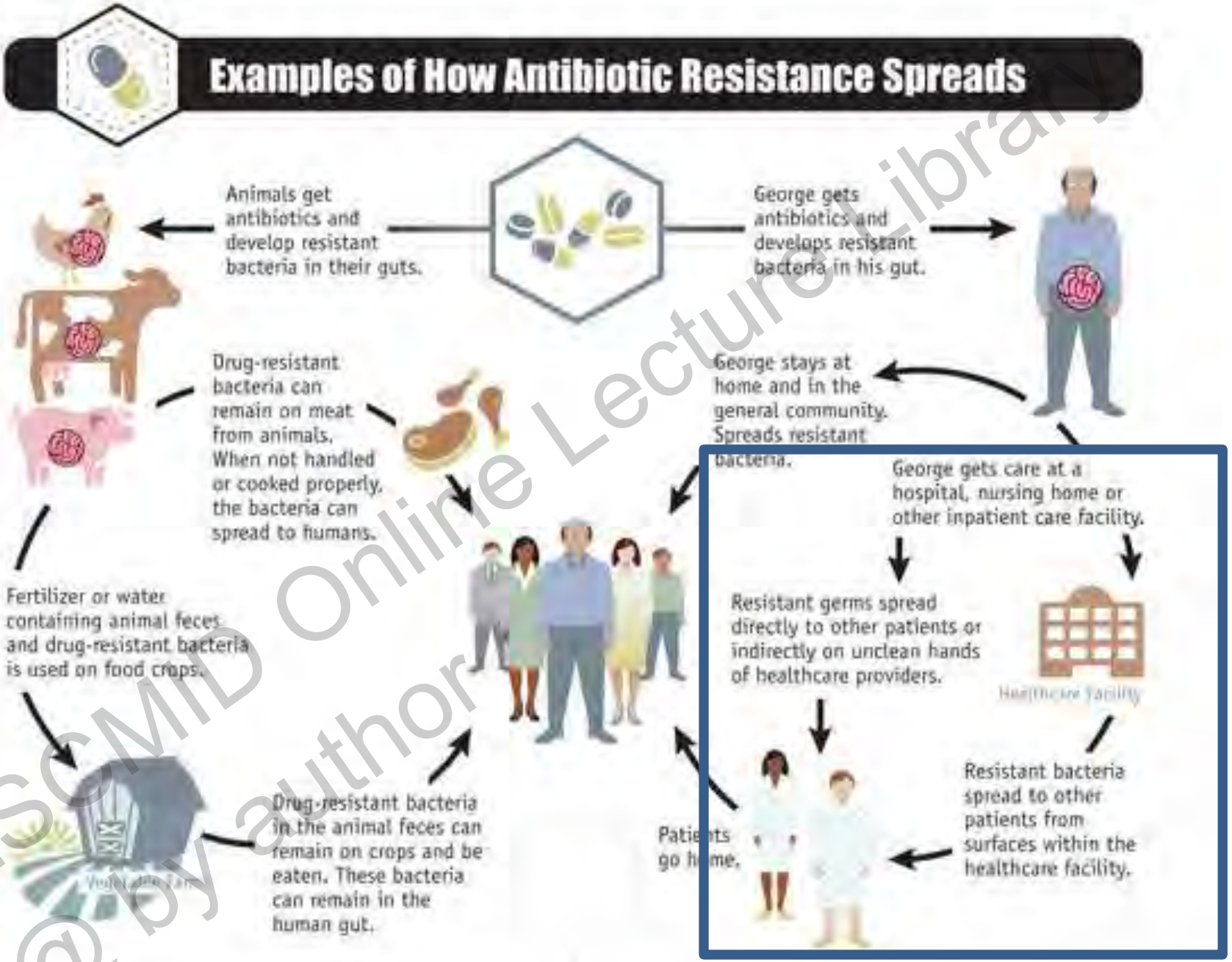
  - Use of probiotics and prebiotics for infection prevention and growth promotion
- Surveillance and **Response**
- Drug Development



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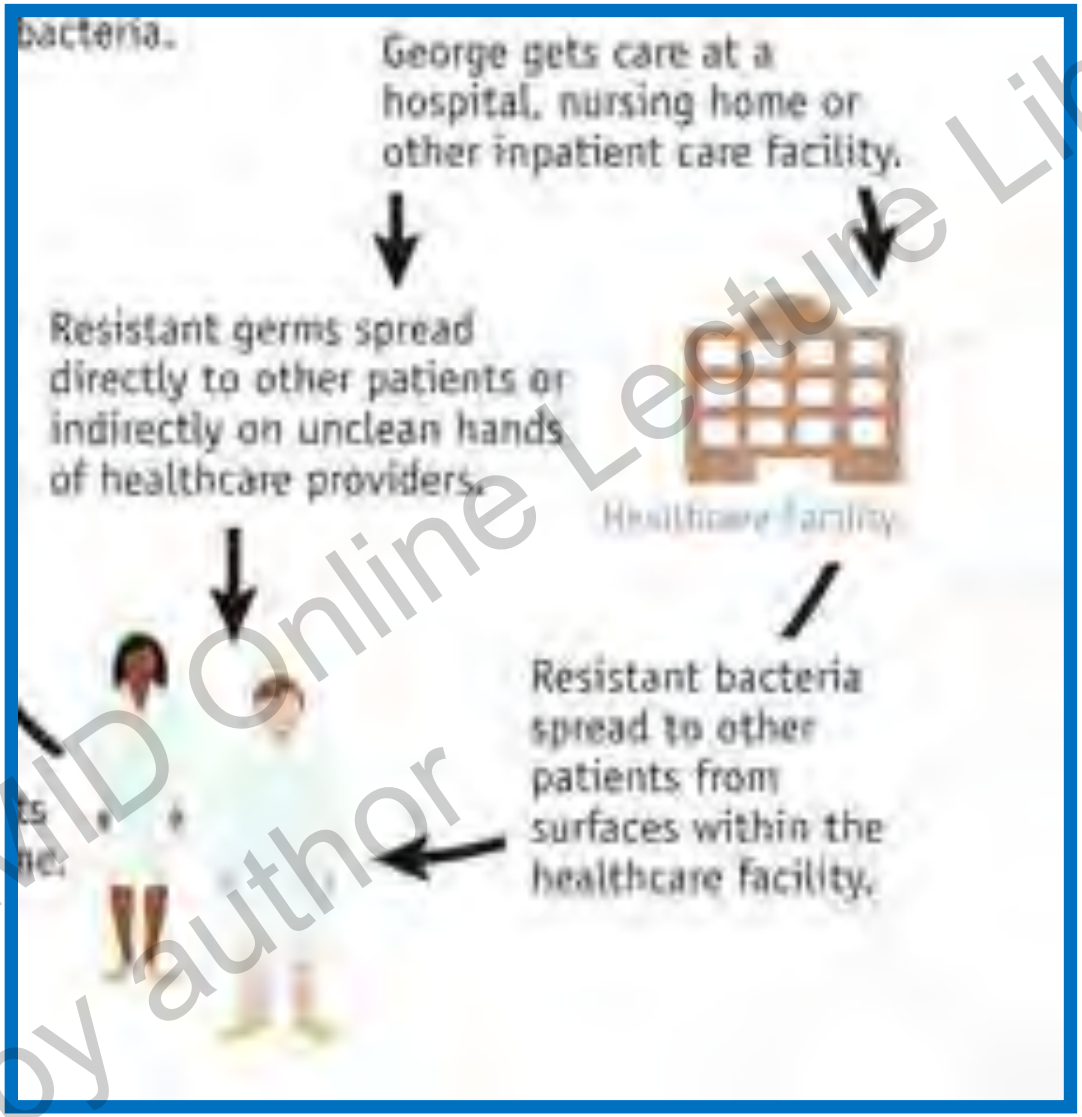

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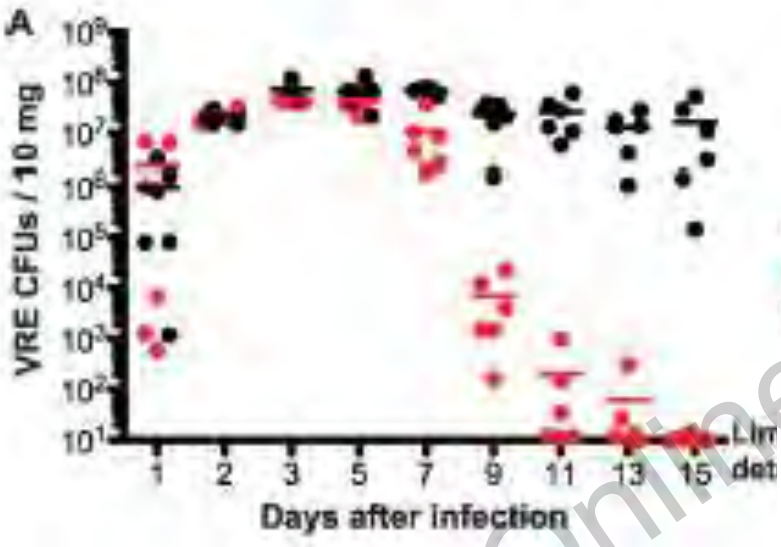
Clearing VRE Colonization in Mice



Ubeda et al, Infection and Immunity, 2012

Use of Stool Transplant to Clear Fecal Colonization with Carbapenem-Resistant *Enterobacteraciae* (CRE):Proof of Concept

Abigail F. Freedman[1,3] and Stephen C. Eppes[2,3]

1. Alfred I. duPont Hospital for Children, Wilmington, DE; 2. Christiana Care Health System, Newark, DE; 3. Sidney Kimmel Medical College of Thomas Jefferson University

- Oct 2010 — Mastoiditis due to *P. aeruginosa*
  Rx: pip/tazo and levofloxacin
- Dec 2010 — Hemophagocytic lymphohistiocytosis
  Rx: High dose steroids
- Jan 2011 — Septic arthritis with bacteremia due to *K. pneumoniae*

Courtesy of Steve Eppes

CHRISTIANA CARE HEALTH SYSTEM

Use of Stool Transplant to Clear Fecal Colonization with Carbapenem-Resistant *Enterobacteraciae* (CRE):Proof of Concept

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- Feb- Oct 2011 — Multiple stool cultures positive for CRE
- Nov 2011 — Osteomyelitis due to *K. pneumoniae*

Courtesy of Steve Eppes

CHRISTIANA CARE HEALTH SYSTEM

Use of Stool Transplant to Clear Fecal Colonization with Carbapenem-Resistant *Enterobacteraciae* (CRE):Proof of Concept

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1. Alfred I. duPont Hospital for Children, Wilmington, DE; 2. Christiana Care Health System, Newark, DE; 3. Sidney Kimmel Medical College of Thomas Jefferson University

- July 2012 — Fecal Microbiota Transplant from younger brother
- Sep 2013 — No further infections or colonization with CRE

Courtesy of Steve Eppes

CHRISTIANA CARE HEALTH SYSTEM

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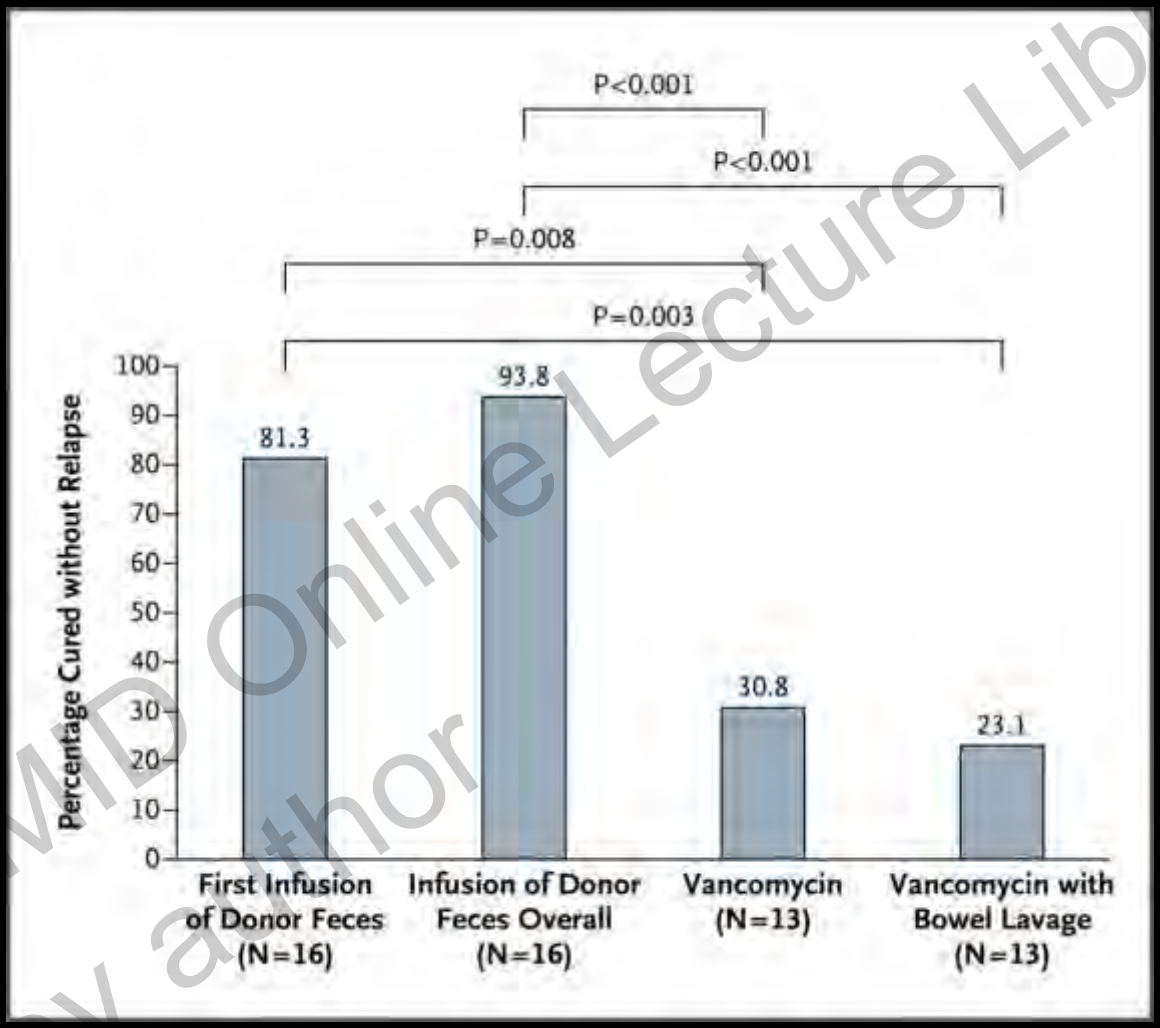
- Human Health Care
  - Auto transplant post antibiotics
- Animal Agriculture
  - Use of pro or prebiotics for infection prevention and growth promotion
- Surveillance and Response
  - Microbiota Transplant for MDRO/CRE
- **Drug Development**

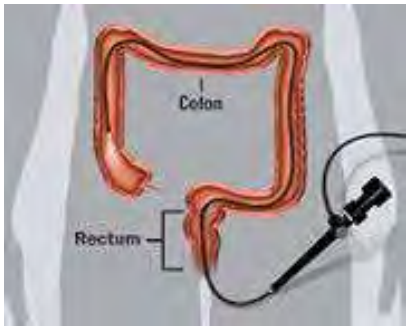
Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.



van Nood E et al. N Engl J Med 2013;368:407-415.

The NEW ENGLAND JOURNAL of MEDICINE

The Evolution of Treatment Options for Recurrent *C. difficile* Infection



Stool Delivery Mechanisms

Rebiotix™
Microbiota Restoration Therapy

SeresHealth
Restoring the Human Microbiome. *Restoring Health.*

Probiotic Mixtures

B-1875a

Ser-109, An Oral, Microbiome-based Therapeutic, Is Efficacious For The Treatment Of Recurrent C. Difficile And Eliminates Enterobacteriacea And Vancomycin-resistant Enterococci Colonizing The Gut

D. S. Pardi[1], C. Kelly[2], S. Khanna[1], C. S. Kraft[3], T. Dhere[3], M. Henn[4], J. G. Aunins[4], **D. N. Cook** [4], R. J. Pomerantz[4], E. L. Hohmann[5]; [1]Mayo, Rochester, MN, [2]Miriam Hosp., Providence, RI, [3]Emory, Atlanta, GA, [4]Seres Hlth., Cambridge, MA, [5]Mass Gen. Hosp., Boston, MA

- SER-109 = a mixture of commensal spores
- Phase I/II study in adults with recurrent *C. difficile* Infection
  - 90-100% clinical cure rate- similar to FMT
  - No drug related SAEs
- Multiple patients with VRE colonization pre therapy had rapid elimination post therapy

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- Animal Agriculture
  - Use of probiotics and prebiotics for infection prevention and growth promotion
- Surveillance and Response
  - Microbiota transplant for MDRO/CRE
- Drug Development
  - Designer probiotics and prebiotics

In conclusion…

- Manipulation of the microbiota composition through
  - Pro-biotics: adds “beneficial” bacteria
  - Pre-biotics: selectively supports “beneficial” bacteria
- will be or already is a new therapeutic approach for preventing the spread of antibiotic resistance