Culture-Independent Diagnostics: Impact on Public Health

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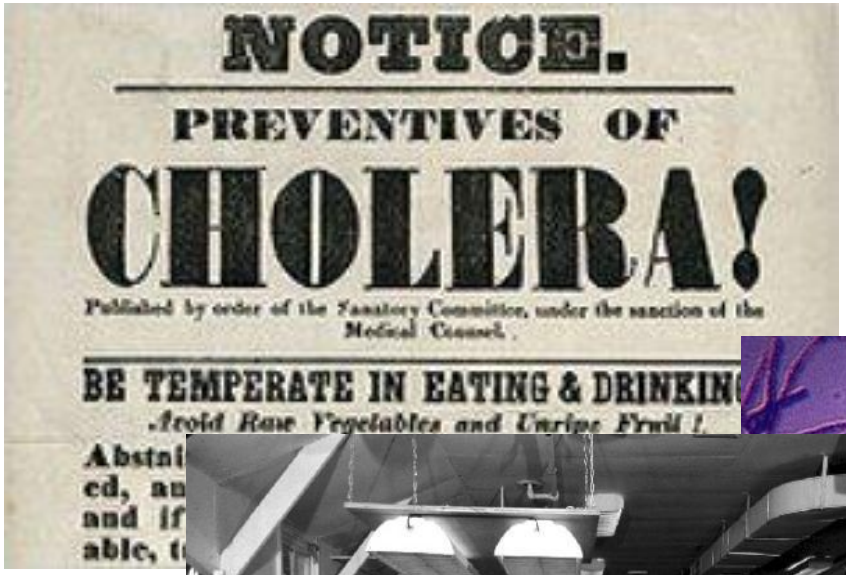
NCEZID/DFWED

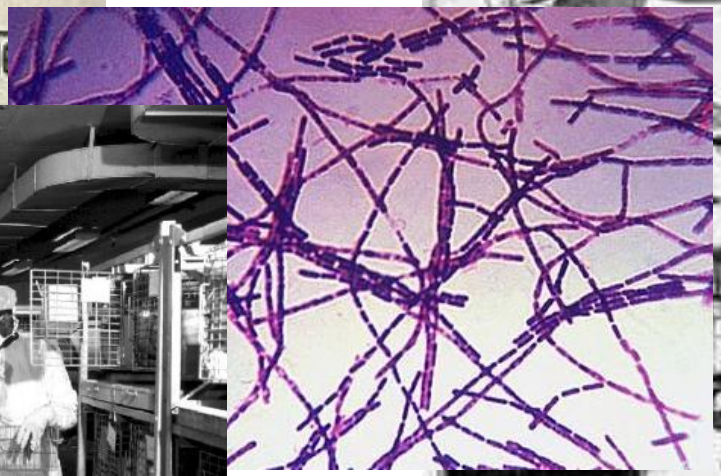
The findings and conclusions in this presentation are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention

Culture-Independent Diagnostics: Impact on Public Health

- Overview of issues
- Strategies for Public Health
- Regulatory role?

Bacterial Culture





Rapid Microbiology Tests

- Available for many conditions, many microbes
  - invasive, respiratory, sexually transmitted, and enteric diseases
  - bacteria, RNA/DNA viruses, parasites, fungi, toxins
- Multiple technologies (nucleic-acid based, antigen-based, metabolite based)
- Multi-analyte panels

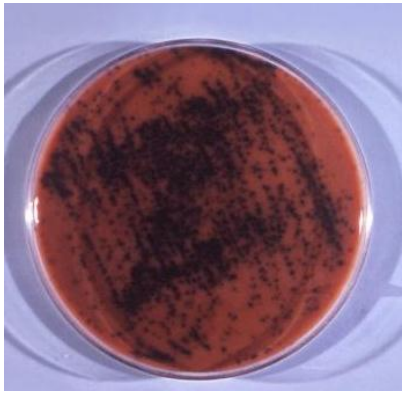
Rapid / Culture-Independent Tests versus Culture

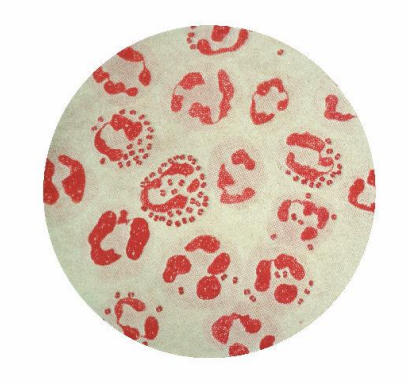
	Culture	Rapid/culture-independent tests
Speed	Slow	Fast
Infrastructure needed	Significant	Minimal
Expertise required	Significant	Minimal
Labor cost	High	Low
Cost of materials	Low	High

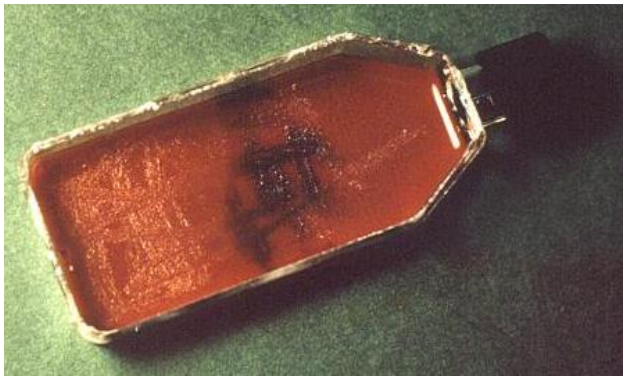
Rapid / Culture-Independent Tests versus Culture

	Culture or standard tests (e.g. microscopy)	Rapid/culture independent tests
Sensitivity	Gold standard	Low to high
Specificity	High	Low to high, almost always different
Interpretation of positive findings	Usually straightforward	Significant issues
Range of pathogens detected	All pathogens allowed by growth or test conditions	Limited to specific pathogen tested
Allows for susceptibility testing & genotyping?	Yes	Generally no

Demise of GC Culture







Rapid NAA test:

- Fast (hours)
- Urine specimen (vs urethral swab)
- Includes *Chlamydia trachomatis*
- High sensitivity

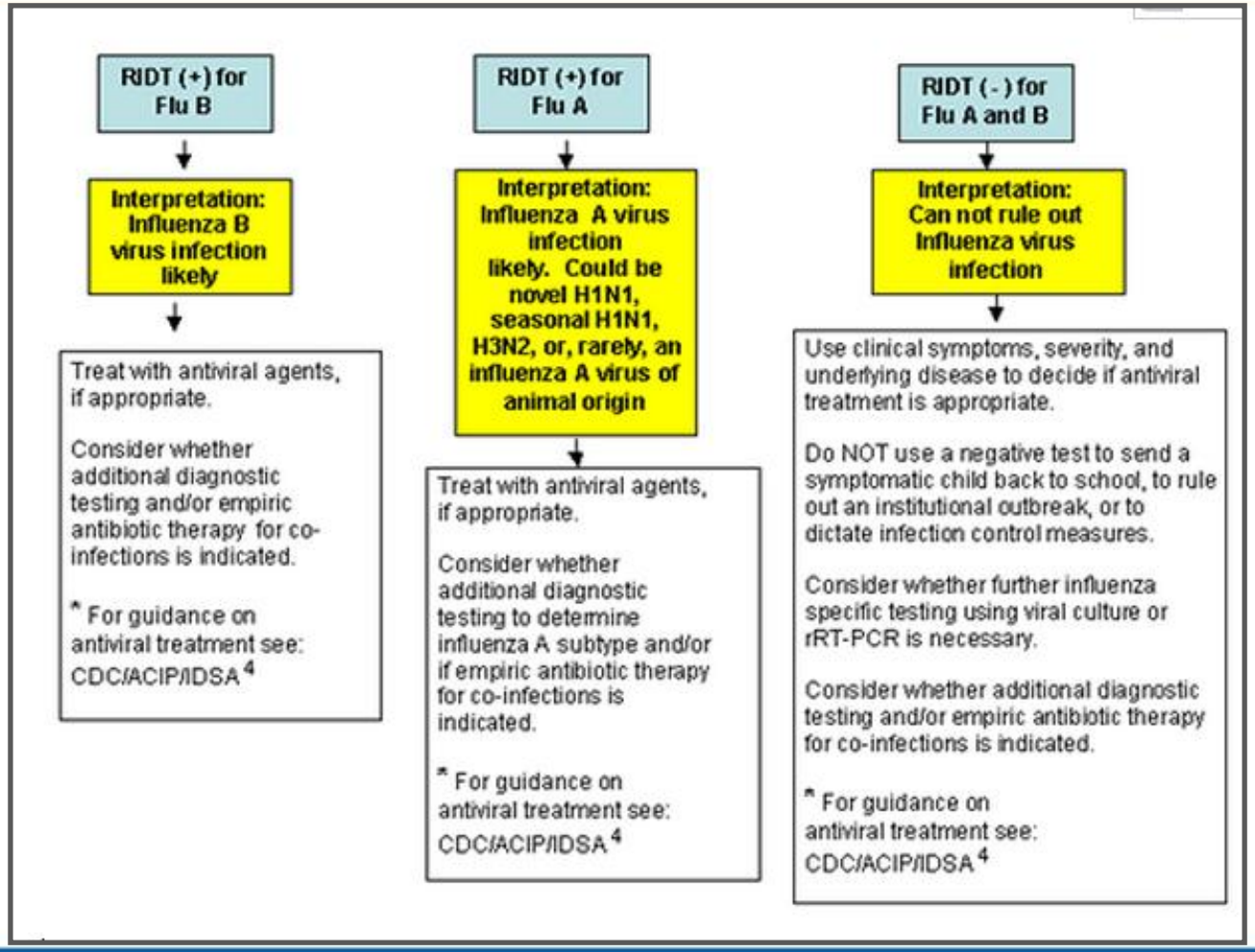
- No susceptibility data
- Specimen incompatible with culture
- Expensive
- Some concerns about false positives

Patient Management

Medical reasons for laboratory testing

- Appropriate treatment
- Prevent unnecessary treatment or procedures

Interim Guidance for the Detection of Novel Influenza A Virus Using Rapid Influenza Diagnostic Tests



http://www.cdc.gov/h1n1flu/guidance/rapid_testing.htm

CDC Home | Search | Health Topics A-Z

MMWR

Recommendations and Reports

October 16, 2009 / 58(RR12);1-14

Recommendations for Diagnosis of Shiga Toxin--Producing *Escherichia coli* Infections by Clinical Laboratories

CDC Home | Search | Health Topics A-Z

MMWR

Weekly

September 29, 2006 / 55(38);1042-1045

Importance of Culture Confirmation of Shiga Toxin-producing *Escherichia coli* Infection as Illustrated by Outbreaks of Gastroenteritis --- New York and North Carolina, 2005

Escherichia coli O157:H7 and other strains of *E. coli* that produce Shiga toxin are collectively known as Shiga toxin-producing *E. coli* (STEC). The current outbreak of STEC O157 infections associated with eating fresh spinach illustrates the importance of obtaining isolates to identify the source of the infections (*1*). Laboratory methods that do not require bacterial culture of stool specimens to identify STEC are being used increasingly by clinical diagnostic laboratories, sometimes without subsequent confirmation of a strain by isolating it in culture. This report describes findings from outbreaks of gastroenteritis in 2005 in New York and North Carolina in which clinical diagnostic laboratories initially used only non-culture methods to detect Shiga toxin (Stx). The findings highlight the importance of confirmation of Stx-positive stool specimens by bacterial culture for timely and reliable identification of STEC infections, including *E. coli* O157 and non-O157 STEC, to enable implementation of appropriate public health actions. An important part of that identification is

Patient Management

Disease Prevention

Patient Manage

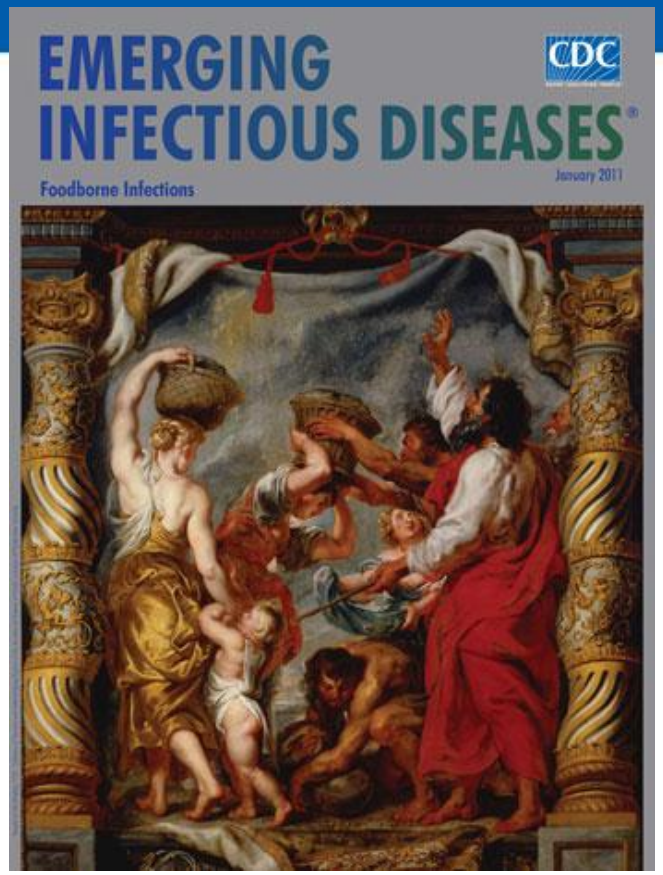
Public health reasons for surveillance / outbreak investigation

- Limit transmission
- Control underlying problems
- Monitor trends → informed policy development

Impacts

- Patient Management
- Public Health Programs
  - Requiring accurate case counts
    - Burden
    - Attribution
    - Trends
  - Isolate-requiring

Estimates of Foodborne Illness



Foodborne Illness Acquired in the United States—Major Pathogens

Elaine Scallan,[1] Robert M. Hoekstra, Frederick J. Angulo, Robert V. Tauxe, Marc-Alain Widdowson, Sharon L. Roy, Jeffery L. Jones, and Patricia M. Griffin

RESEARCH

Foodborne Illness Acquired in the United States—Unspecified Agents

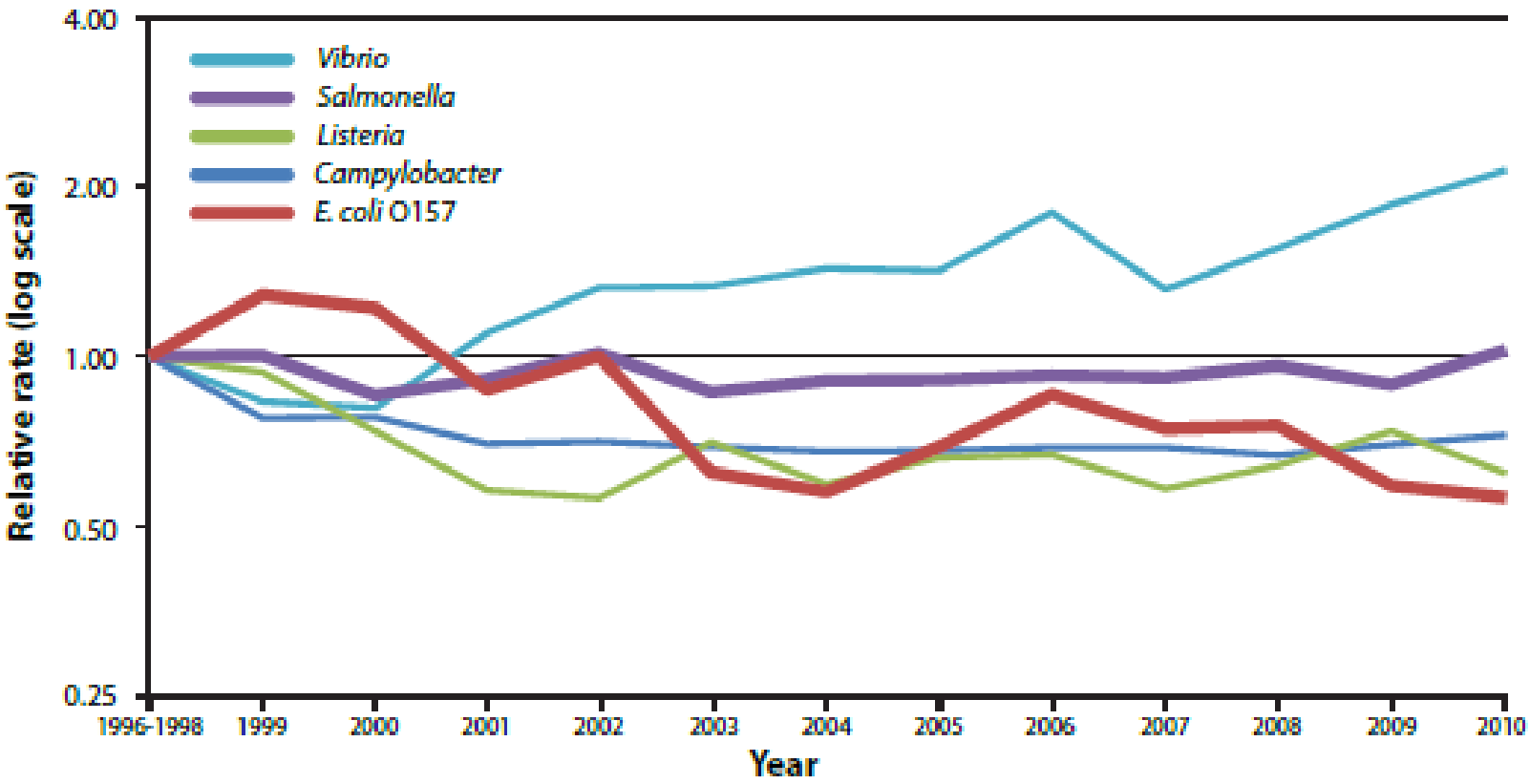
Elaine Scallan,[1] Patricia M. Griffin, Frederick J. Angulo, Robert V. Tauxe, and Robert M. Hoekstra

COMMENTARY

How Safe Is Our Food?

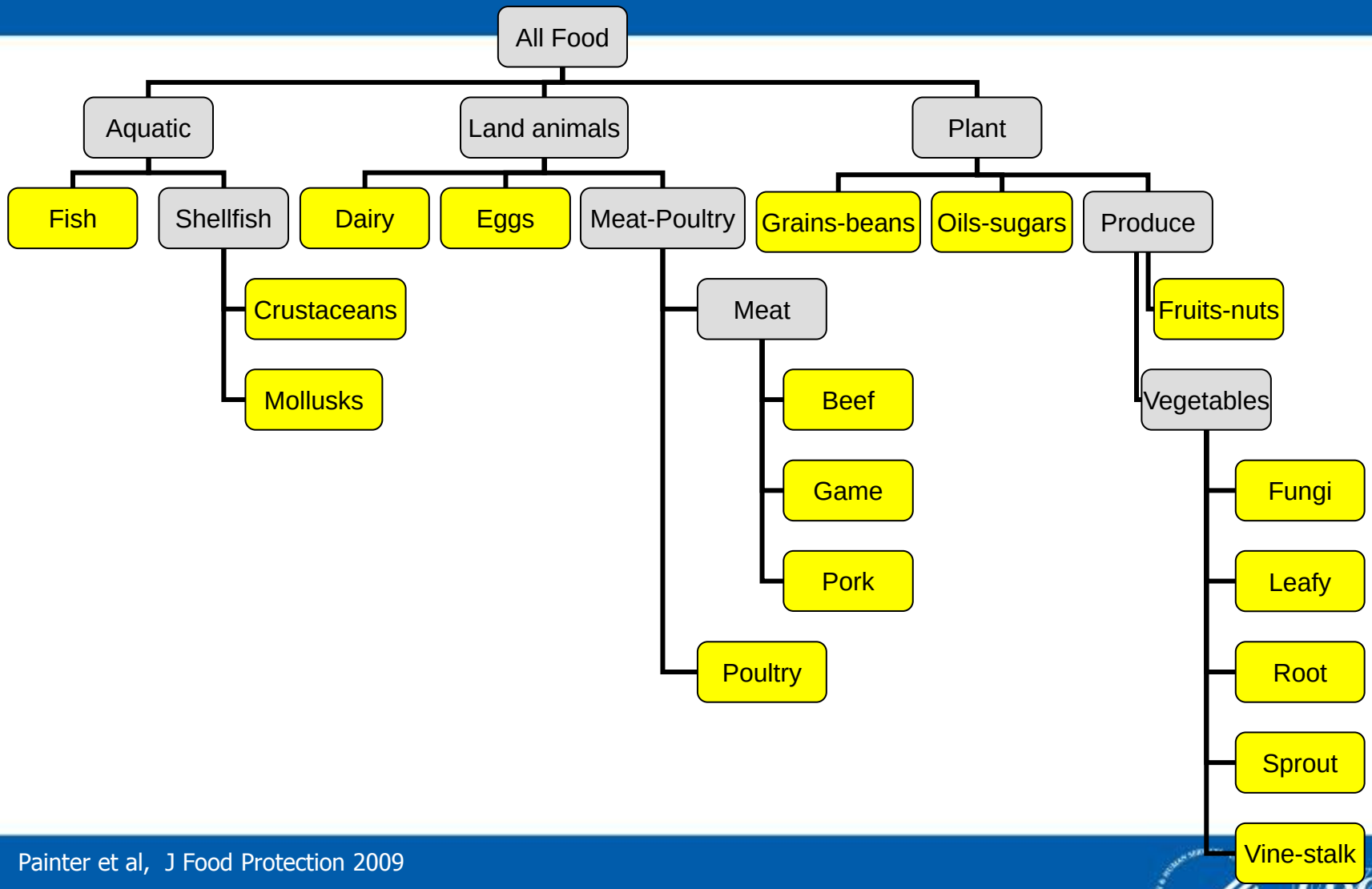
J. Glenn Morris, Jr.

Relative rates of laboratory-confirmed infections with *Campylobacter*, *E. coli* O157, *Listeria*, *Salmonella*, and *Vibrio* compared with 1996-1998 rates, by year – Foodborne Diseases Active Surveillance Network (FoodNet), United States, 1996-2010†



† The position of each line indicates the relative change in the incidence of that pathogen compared with 1996-1998. The actual incidences of these infections cannot be determined from this graph.

Hierarchical scheme for categorizing foods into commodities



Painter et al, J Food Protection 2009

Addressing CIDT: Burden, Attribution, Trends

- Determine extent of issue
- Study test performance
- Redefine case definitions

Impacts

- Patient Management
- Public Health Programs
  - Requiring accurate case counts
    - Burden
    - Attribution
    - Trends
  - Isolate-requiring
    - Subtype-based tracking programs
    - Susceptibility monitoring
    - Subtype-based attribution studies

Selected Microbial Disease Agents Under Surveillance

Agent	Public health surveillance	Isolate significance
Salmonella spp.	Subtype, AST	++++
Shigatoxin-producing *E. coli*	Subtype, AST	++++
Listeria monocytogenes	Subtype, AST	++++
Mycobacterium tuberculosis	Genotype, AST	++++
Bordetella pertussis	AST	+++
Neisseria meningitidis	Subtype, AST	+++
Legionella pneumophila	Subtype (outbreaks)	++
Influenza virus	Serotype, AST	++
Neisseria gonorrhea	AST	+
Methicillin-resistant *Staphylococcus aureus*	Subtype (outbreaks)	+
Cryptococcus neoformans	AST	?

CDC Vitalsigns™

June 2011

Making Food Safer to Eat

Reducing contamination from the farm to the table

1 in 6

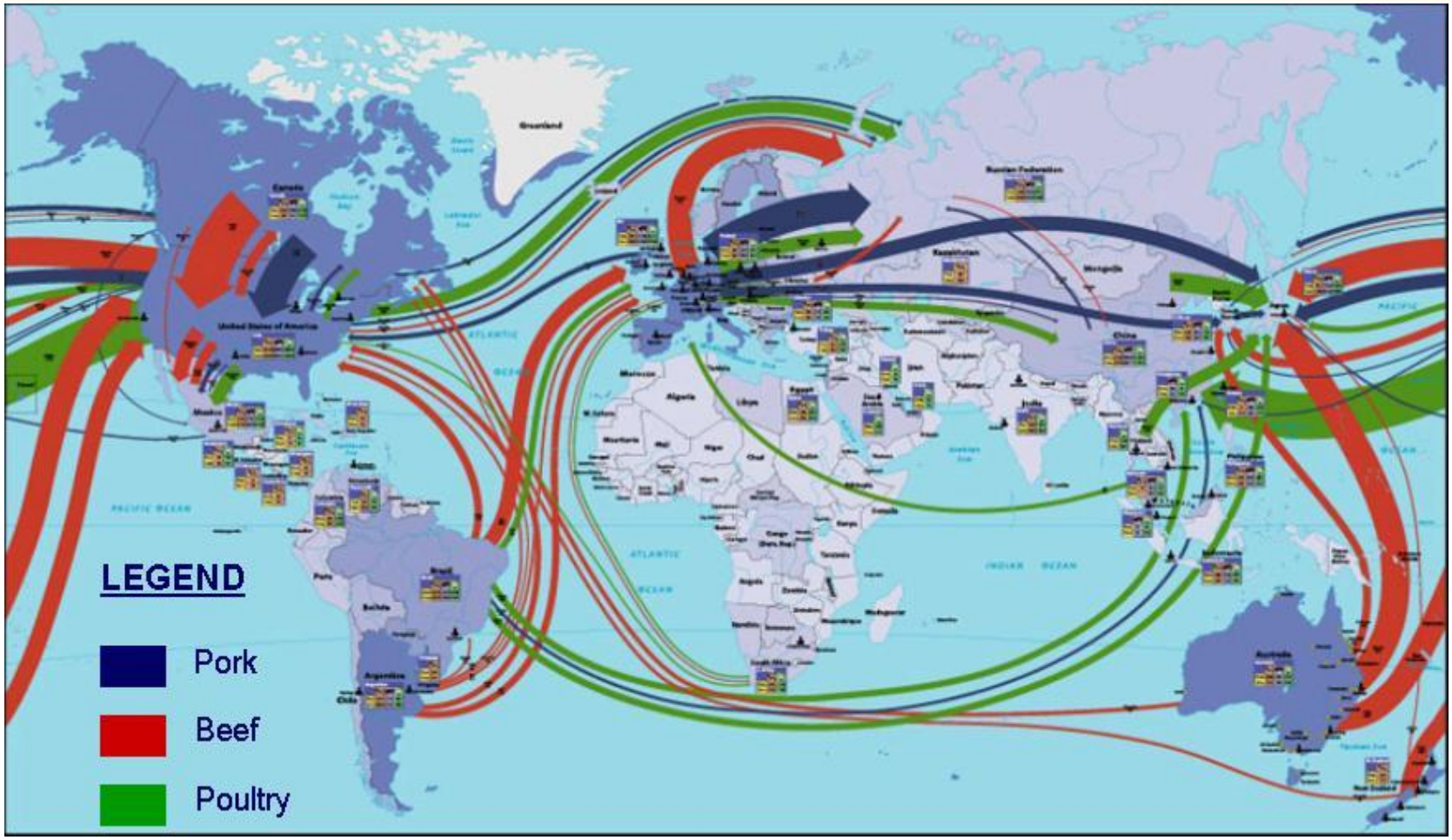
About 1 in 6 (or 48 million) people gets sick each year from contaminated food.

50%

E. coli O157 infections have been cut about in half

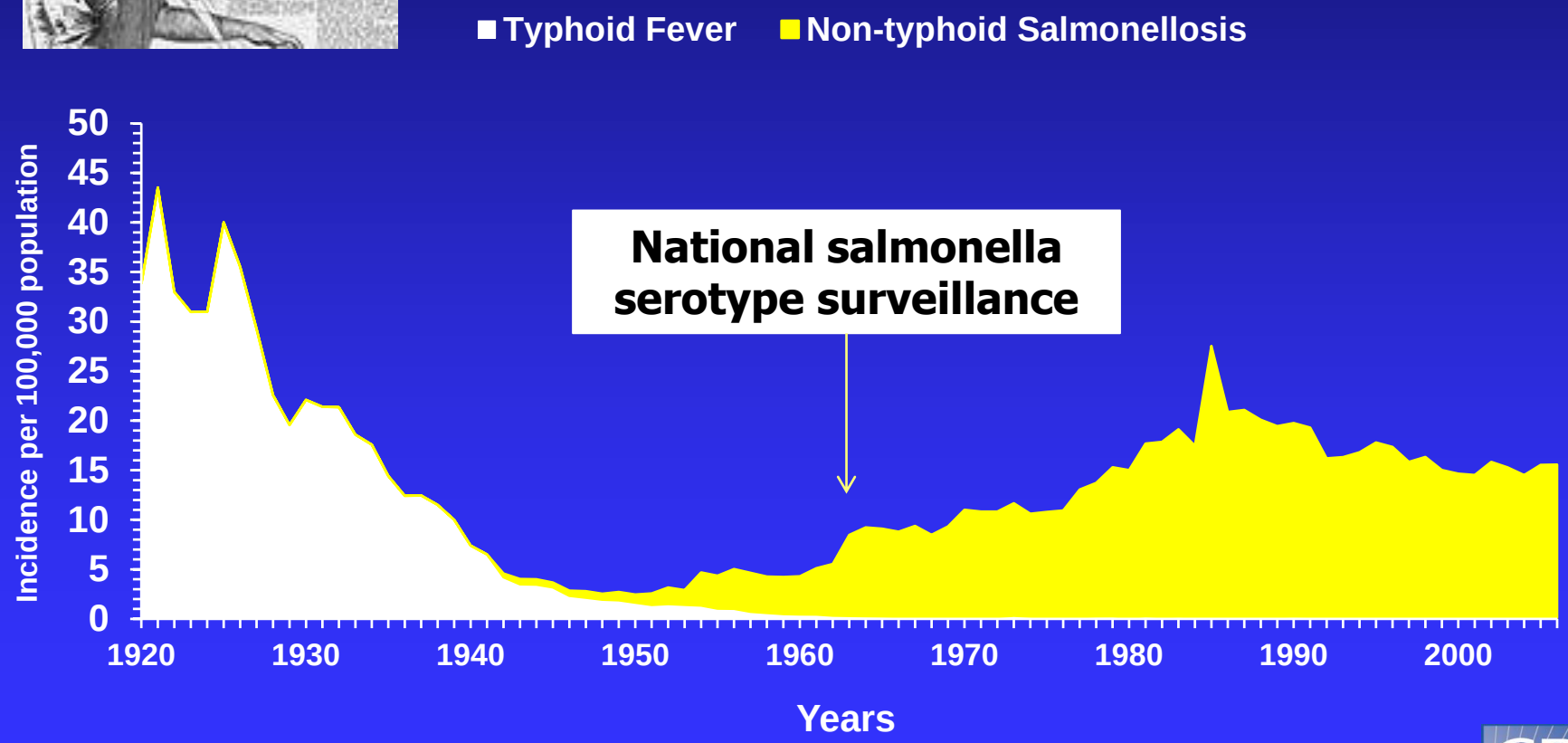
Each year, roughly 1 in 6 people in the US gets sick from eating contaminated food. The 1,000 or more reported outbreaks that happen each year reveal familiar culprits—*Salmonella* and other common germs. We know that reducing contamination works. During the past 15 years, a dangerous type of *E. coli* infection, responsible for the recall of millions of pounds of ground beef, has been cut almost in half. Yet during that same time, *Salmonella* infection, which causes more hospitalizations and deaths than any other type of germ found in food and $365 million in direct medical costs annually, has not declined. Each year, 1 million

Global Meat Trade



Source: Center for Global Food Issues

Nationwide reporting began in 1912
Reported *Salmonella* infections in the United States, 1920-2006



CDC, National surveillance data

CDC
Centers for Disease Control and Prevention

Salmonella Serotype Surveillance

Original Article

A National Outbreak of *Salmonella enteritidis* Infections from Ice Cream

Thomas W. Hennessy, M.D., Craig W. Hedberg, Ph.D., Laurence Slutsker, M.D., M.P.H., Karen E. White, M.P.H., John M. Besser-Wiek, M.S., Michael E. Moen, M.P.H., John Feldman, B.S., William W. Coleman, M.S., Larry M. Edmonson, M.P.H., Kristine L. MacDonald, M.D., M.P.H., and Michael T. Osterholm, Ph.D., M.P.H.

N Engl J Med 1996; 334:1281-1286 May 16, 1996

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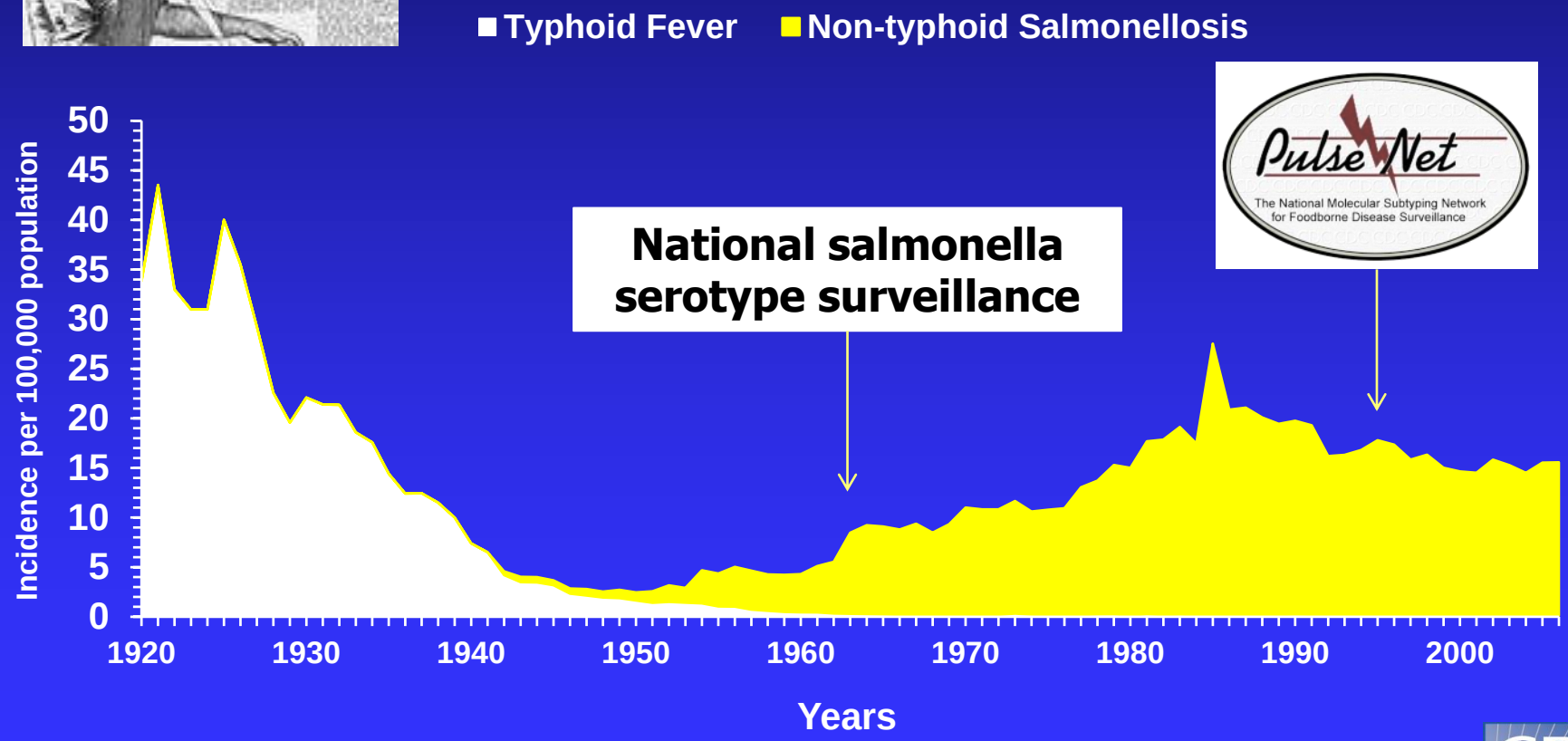


CDC, National surveillance data

CDC
Centers for Disease Control and Prevention

87 labs in the PulseNet USA network

December 2011

The decade's 10 biggest food-borne illness outbreaks (from CNN)

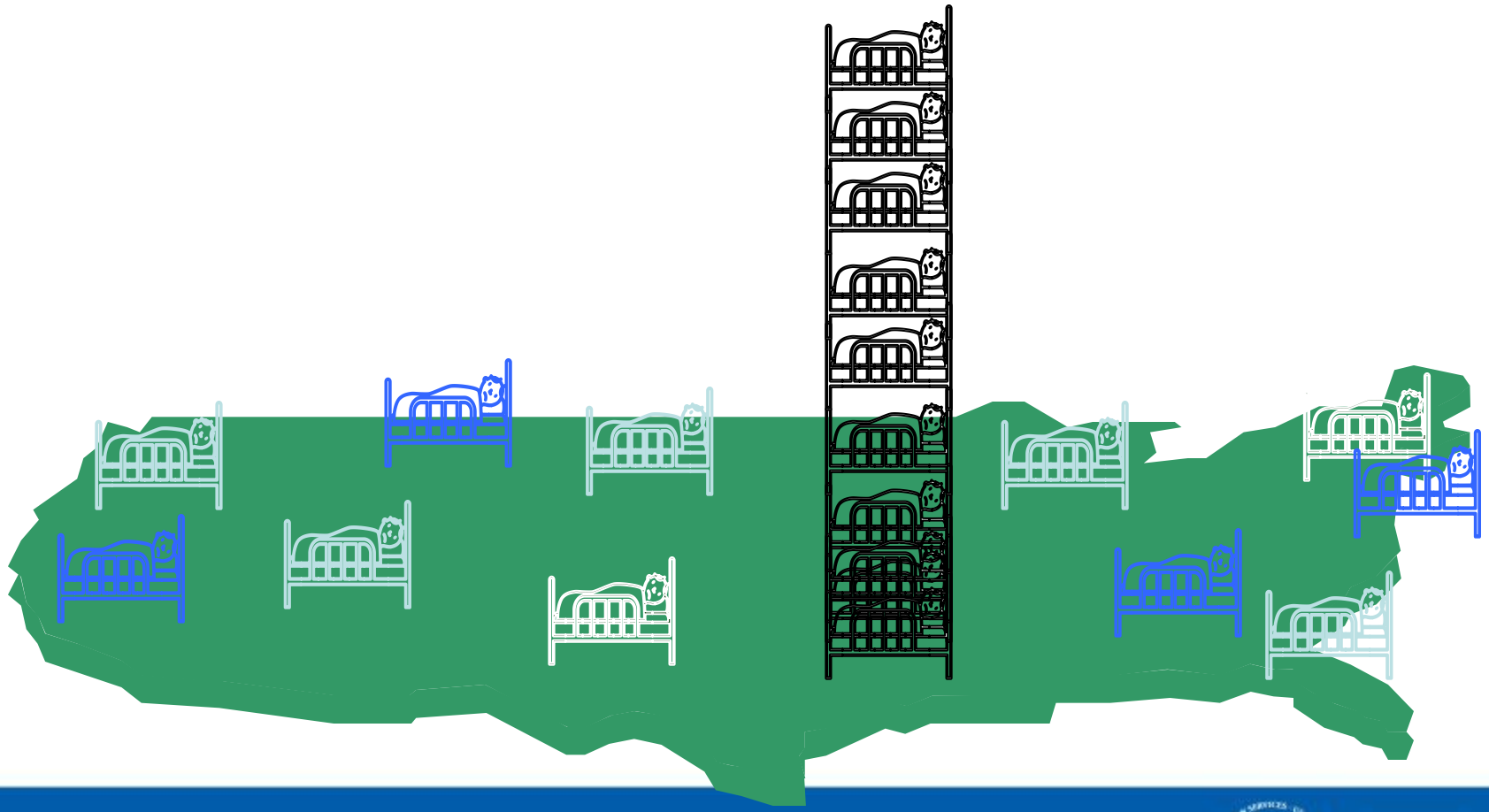
By **Jacque Wilson**, CNN
updated 8:00 AM EDT, Thu November 3, 2011

1. 2011: Cantaloupes (*Listeria monocytogenes*)
2. 2011: Turkey (*Salmonella*)
3. 2010: Eggs (*Salmonella*)
4. 2010: Celery (*Listeria monocytogenes*)
5. 2008: Jalapeno and Serrano peppers (*Salmonella*)
6. 2008 – 2009: Peanut butter (and peanut-containing products; *Salmonella*)
7. 2006: Spinach (bagged; *E. coli* O157:H7)
8. 2005 – 2006: Tomatoes (4 outbreaks; *Salmonella*)
9. 2004: Tomatoes (*Salmonella*)
10. 2002: Deli meat (*Listeria monocytogenes*)
11. 2001: Cantaloupe (*Salmonella*)

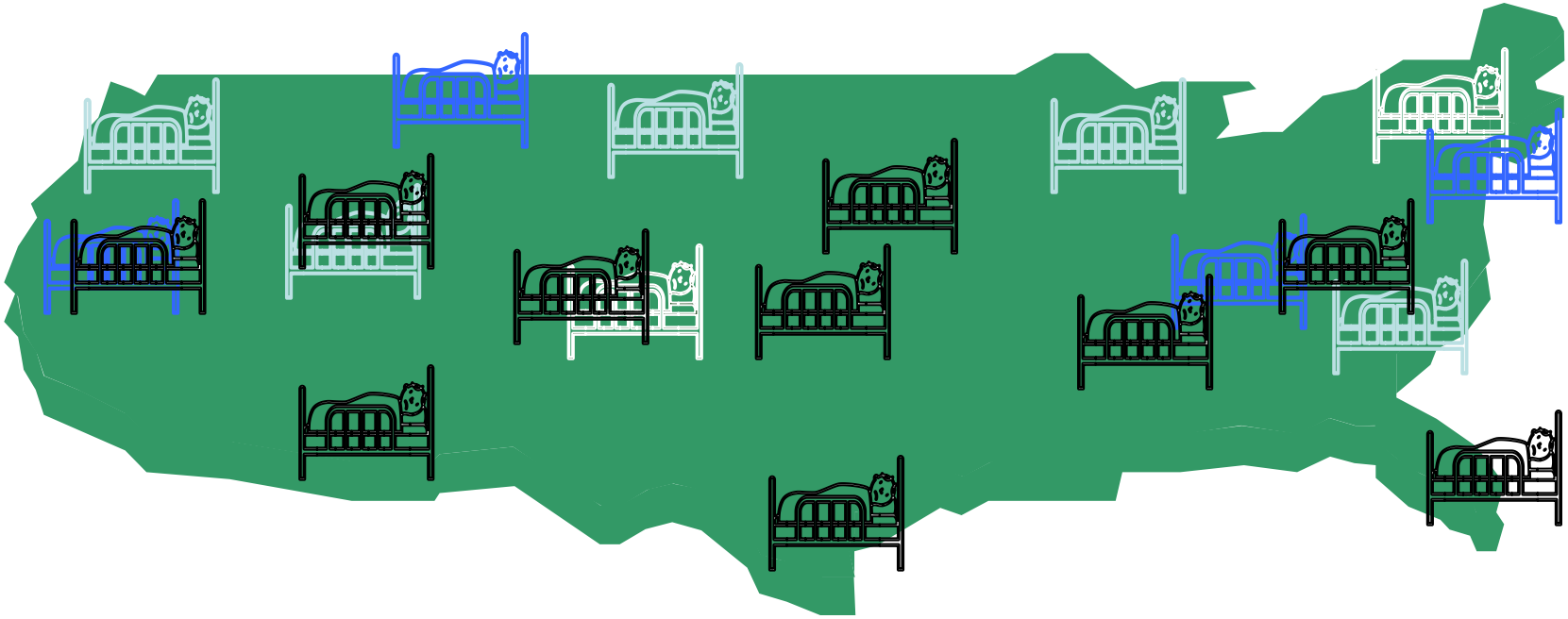
Multistate Foodborne Outbreak Investigations, 2012 (so far)

- Ground Beef - *Salmonella* Enteritidis
- Live Poultry - *Salmonella* Hadar
- Live Poultry - *Salmonella* Montevideo
- Multistate Outbreak – *Escherichia coli* O145 Infections
- Live Poultry - *Salmonella* Infantis, Newport, and Lille
- Dry Dog Food - *Salmonella* Infantis
- Raw Scraped Ground Tuna Product - *Salmonella* Bareilly and *Salmonella* Nchanga
- Small Turtles - *Salmonella* Sandiego, *Salmonella* Pomona, and *Salmonella* Poona
- Raw Clover Sprouts at Jimmy John's Restaurants -*Escherichia coli* O26
- Restaurant Chain A - *Salmonella* Enteritidis

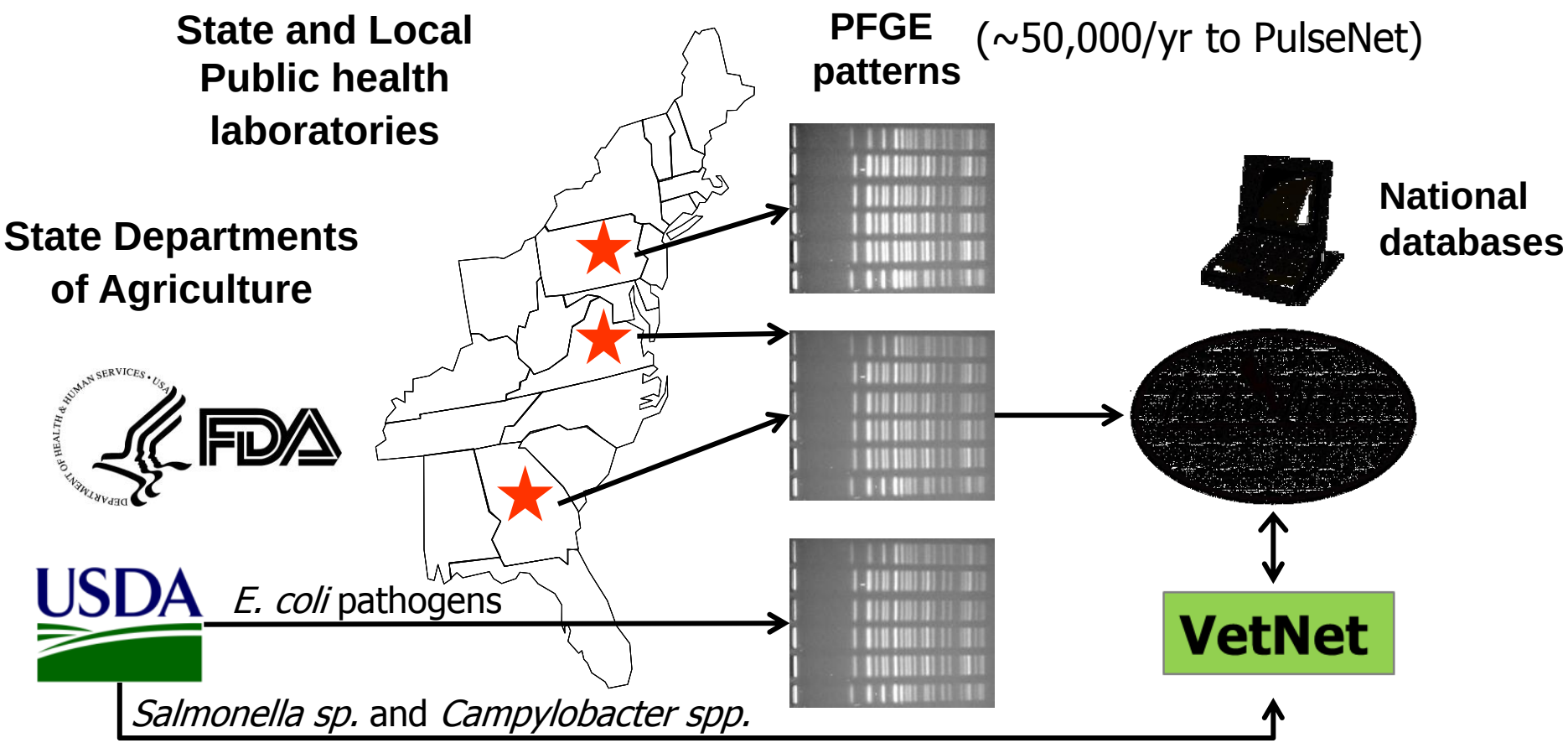
A large outbreak in one place may be obvious



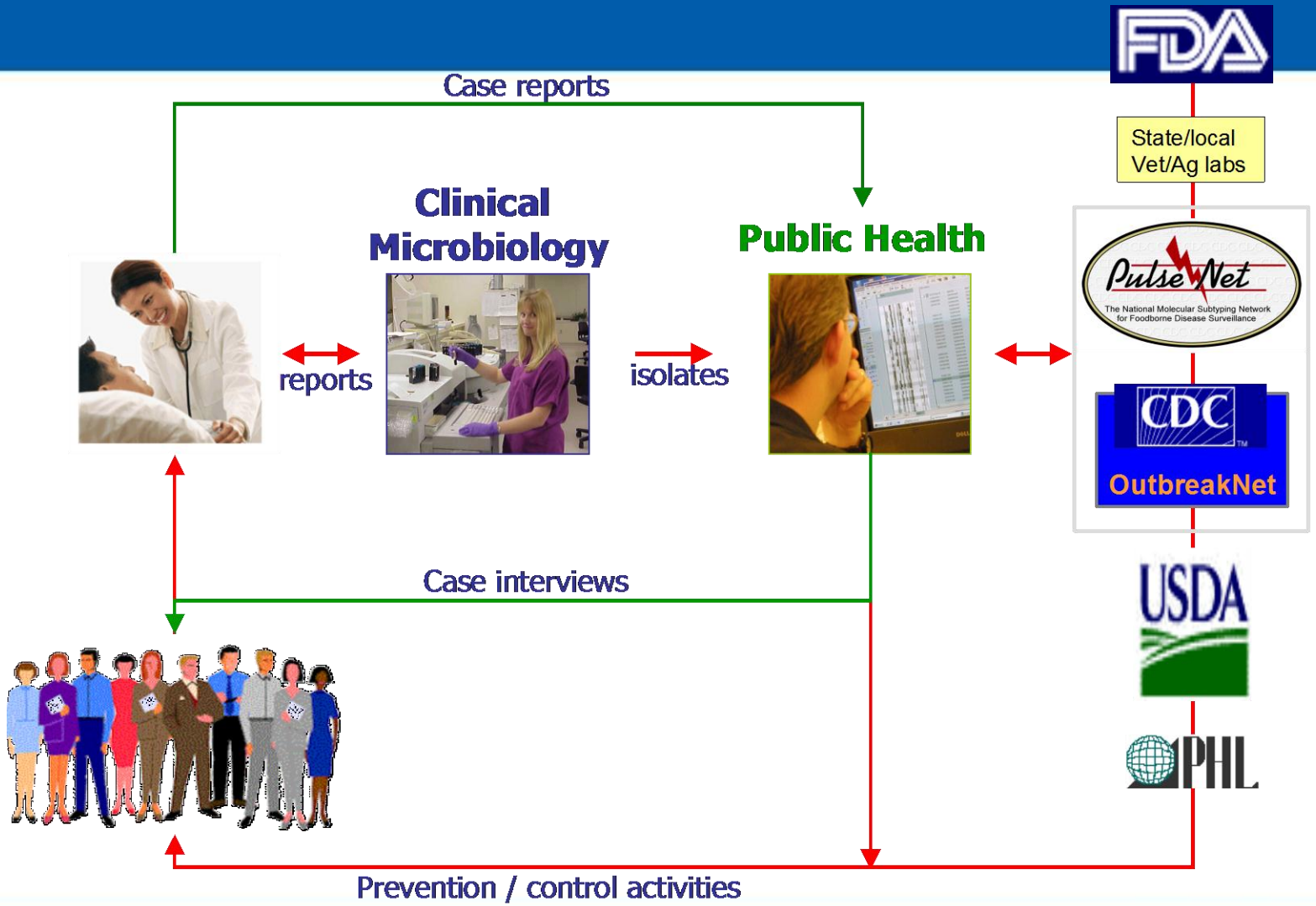
An outbreak with persons in many places may be difficult to detect, unless cases can be linked



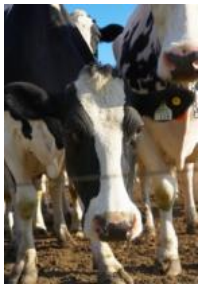
PulseNet/VetNet Electronic Communication



Pathogen Specific Surveillance



Preventing Foodborne Disease

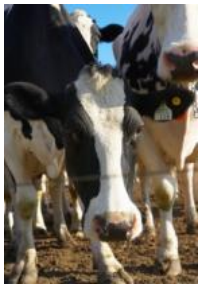


Farm

Transport
Processing
Distribution

Preparation

Preventing Foodborne Disease



Farm

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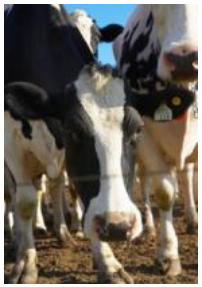
Disease surveillance

Preventing Foodborne Disease



Farm

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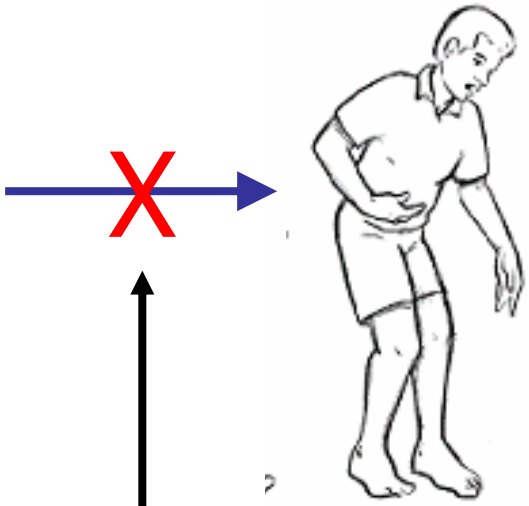


Disease surveillance

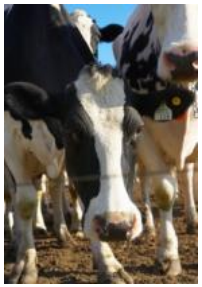
Limit ongoing illness

Largest U.S. Food Recalls in which PulseNet Played a Prominent Role

Year	Pathogen	Food	Amount recalled
2011	*Listeria monocytogenes*	Cantaloupe	Unknown
2011	*Salmonella* Heidelberg	Ground turkey products	>36,000,000 lbs
2010	*Salmonella* Enteritidis	Shell eggs	>500,000,000 eggs
2010	*Salmonella* Montevideo	Ready-to-eat Italian sausage products/pepper	>1,263,754 lbs
2009	*E. coli* O157:H7	Cookie dough	300,000 cases of product
2009	*Salmonella* Typhimurium	Peanut butter/peanut products	>3000 types of products
2008	*E. coli* O157:H7	Ground beef	5,300,000 Ibs
2007	*Salmonella* I 4,5,12:i:-	Frozen pot pies	Millions of pot pies
2007	*E. coli* O157:H7	Frozen pizza	5,000,000 pizzas
2007	*E. coli* O157:H7	Ground beef (3 outbreaks)	35,400,000 lbs
2006	*Salmonella* Tennessee	Peanut butter	326,000,000 lbs
2004	*Salmonella* Enteritidis	Raw almonds	13,000,000 lbs
2003/'09	*E. coli* O157:H7	Blade Tenderized Frozen Steak	865,046 lbs
2002	*Listeria monocytogenes*	Ready-to-eat poultry products	27,400,000 lbs
2002	*E. coli* O157:H7	Ground beef	18,600,000 lbs
2000	*Listeria monocytogenes*	Ready-to-eat poultry products	16,900,000 lbs
2000	*E. coli* O157:H7	Ground beef	1,100,000 lbs
1998	*Listeria monocytogenes*	Hot dogs, deli meats	35,000,000 lbs
1998/'08	*Salmonella* Agona	Toasted oats cereal	>3,000,000 lbs
1997	*E. coli* O157:H7	Frozen ground beef	25,000,000 lbs

Courtesy J. Besser

Preventing Foodborne Disease



Farm

Transport
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Distribution

Preparation

Disease surveillance

Limit ongoing illness

fix underlying problems

Industries Stimulated to Change by PulseNet-Triggered Investigations

Peanut products

Ready-to-eat & "ready-to cook" foods

Eggs

Beef

Leafy greens

Other vegetables

Tree nuts

Spices

Sprouts

Mellon

Poultry

"The foodborne disease surveillance system is to the food industry what radar is to automobile drivers – It is the "threat" of being caught that helps drive compliance with best safety practices."

from Mike Doyle, Ph.D;
CDC Public Health Grand Rounds November 2009

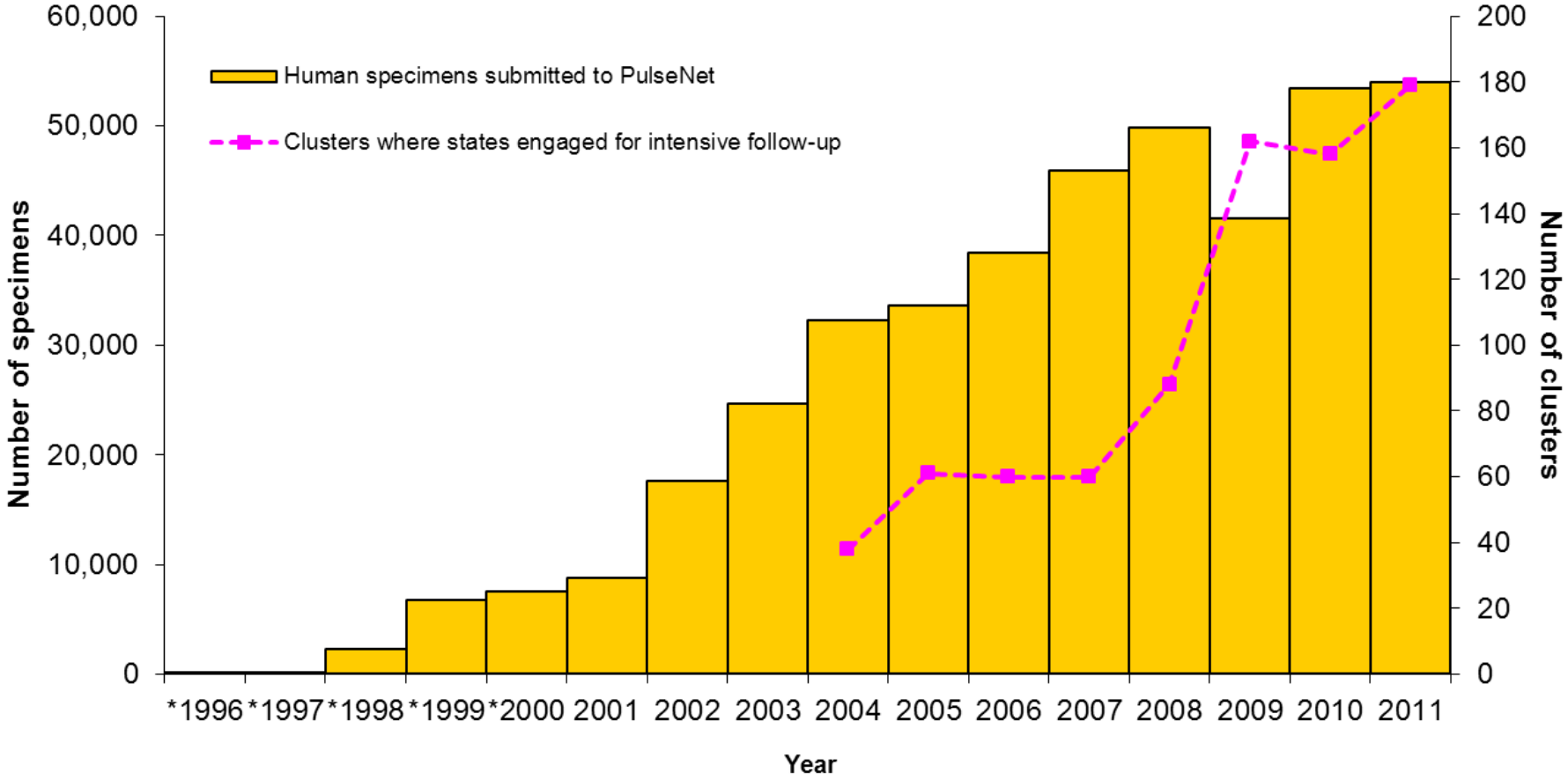
Under-appreciated Sources of Infection

- *Salmonella* in reptiles and amphibians
- Multiple pathogens from live bird markets
- *Salmonella* from microbiology lab exposure
- *Salmonella* in "feeder" mice
- *Vibrio vulnificus* after fish handling
- *Salmonella* in baby chicks and ducks
- *Salmonella* in owl pellets
- STEC in petting zoos

PulseNet Protocols

- *E. coli* O157
- Non-O157 STEC (VTEC)
- *Salmonella*
- *Shigella*
- *Listeria monocytogenes*
- *Vibrio cholerae*
- *Vibrio parahaemolyticus*
- *Campylobacter jejuni/coli*
- *Clostridium perfringens*
- *Clostridium botulinum*
- *Yersinia pestis*

Bacterial isolates from humans uploaded to PulseNet USA, and identified clusters, 1996-2011†

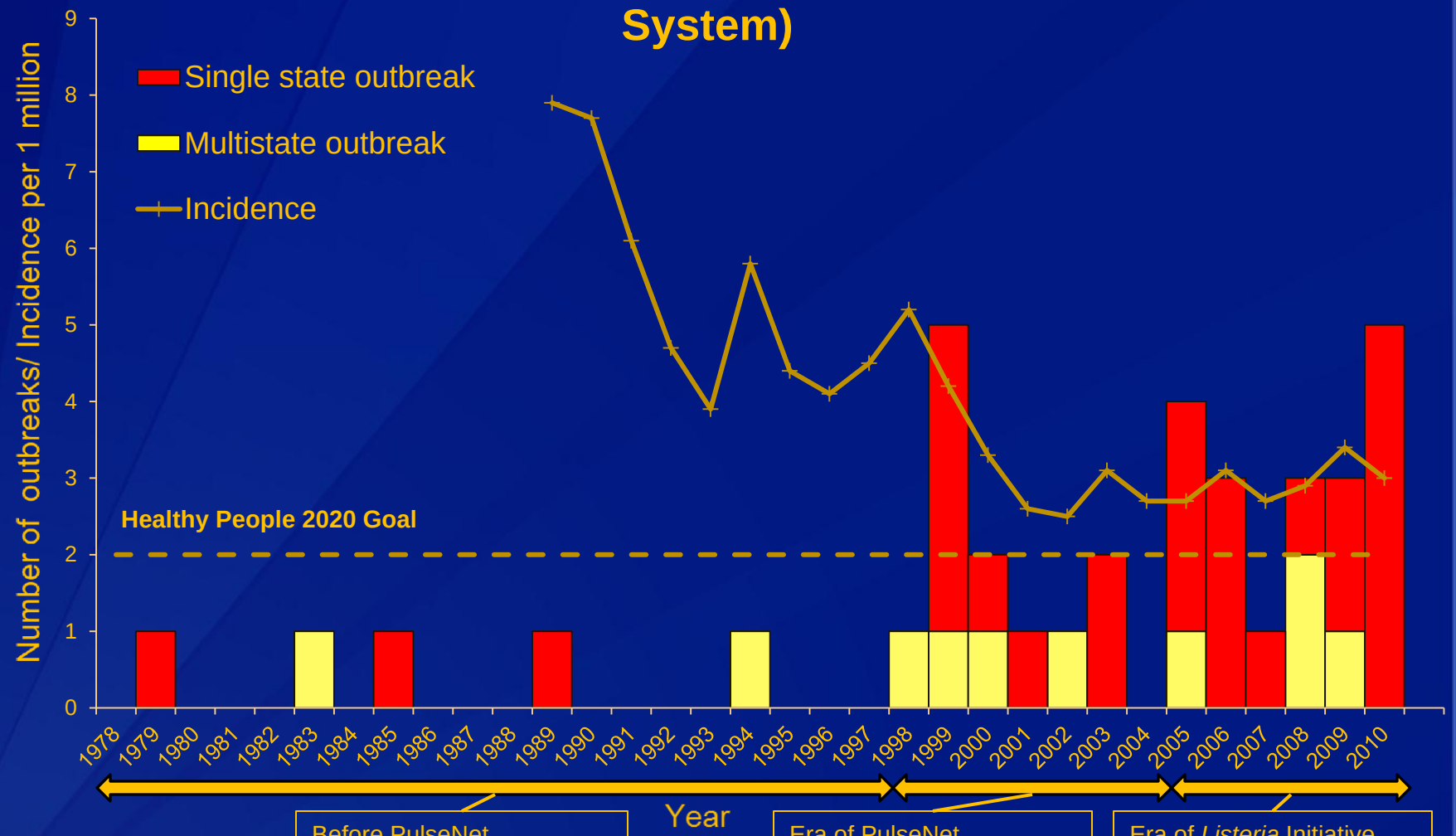


† Data are preliminary and subject to change
* data type information may not be complete for these years

PulseNet-Based Surveillance

- **Each year PulseNet U.S.A. identifies**
  - ~1,500 clusters at local/state level
  - 200 multi-state clusters investigated

Incidence and Outbreaks of *Listeria*, 1978-2010
(from FoodNet and Foodborne Disease Outbreak Surveillance System)



Before PulseNet
1978-1997 (20 years)
5 outbreaks (2 multistate)
Average **54** cases/outbreak

Era of PulseNet
1998-2004 (7 years)
13 outbreaks (4 multistate)
Average **22** cases/outbreak

Era of *Listeria* Initiative
2005-2010 (6 years)
19 outbreaks (4 multistate)
Average **18** cases/outbreak

Dispatches

Costs and Benefits of a Subtype-Specific Surveillance System for Identifying *Escherichia coli* O157:H7 Outbreaks

Elamin H. Elbasha,* Thomas D. Fitzsimmons,*† and Martin I. Meltzer*
*Centers for Disease Control and Prevention, Atlanta, Georgia, USA; and †Colorado Department of Public Health and Environment, Denver, Colorado, USA

We assessed the societal costs and benefits of a subtype-specific surveillance system for identifying outbreak-associated *Escherichia coli* O157:H7 infections. Using data from Colorado, we estimated that if it averted five cases annually, the system would recover all its costs.

Escherichia coli O157:H7 infections pose a

nationally. After the outbreak was traced to the

83 member countries from 7 national and regional PulseNet networks

December 2011

International outbreak of *E. coli* O157 infections linked to ground beef patties of a particular brand

CDC, October 26, 2007

A joint investigation between the Canadian Food
rtment of
ion Service
of a multi-
57:h7
n the USA,
anadian beef-producing firm. The outbreak was significant in

International Outbreaks of shigellosis in Denmark and Australia in 2007 associated with imported baby corn from Thailand

By author name and date

Two outbreaks of *Shigella sonnei* infections simultaneously detected in Denmark and Australia were found to be linked to the same baby corn packing house in Thailand. PulseNet played a key role in confirming this link when

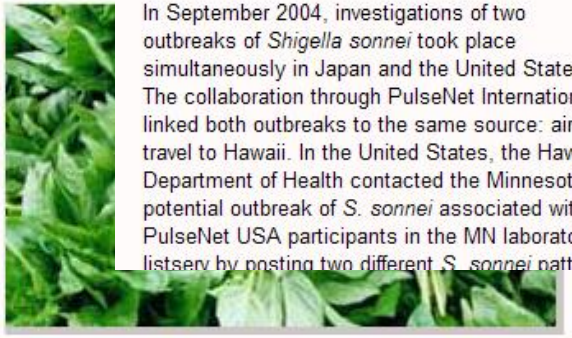
International outbreak of *Shigella sonnei* associated with air travel to Hawaii in 2004

By multiple authors, Japan Journal of Infectious Diseases, July 13, 2006

In September 2004, investigations of two outbreaks of *Shigella sonnei* took place simultaneously in Japan and the United States. The collaboration through PulseNet International linked both outbreaks to the same source: air travel to Hawaii. In the United States, the Hawaii Department of Health contacted the Minnesota Department of Health (MN) to inform them of a potential outbreak of *S. sonnei* associated with domestic and international air travel to Hawaii. PulseNet USA participants in the MN laboratory alerted the rest of PulseNet USA via the PulseNet listserv by posting two different *S. sonnei* patterns digested with XbaI that were obtained from

International outbreak of *Salmonella* Senftenberg infection in 2007 associated with consumption of fresh basil imported from Israel

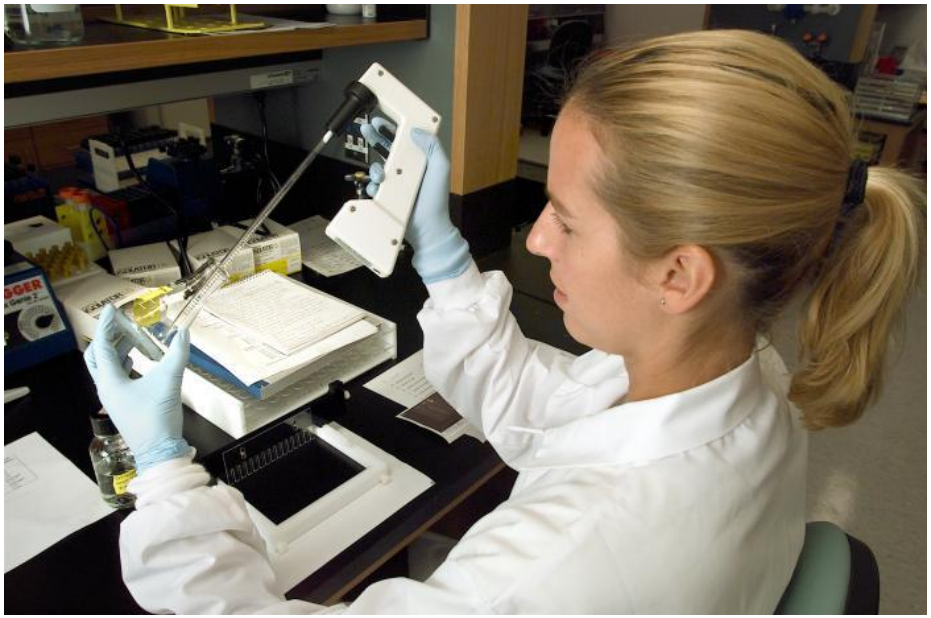
Multiple authors, Eurosurveillance, Volume 12, Issue 24, 14 June 2007



PFGE analysis performed according to the PulseNet *Salmonella* protocol by researchers in Europe and the United States, and shared through the PulseNet International network and the former European Enter-net, was instrumental in delineating this outbreak caused by *Salmonella* Senftenberg and confirming its source: fresh basil from Israel. Read original

Current PulseNet Methods (PFGE and MLVA) are Isolate-Dependent

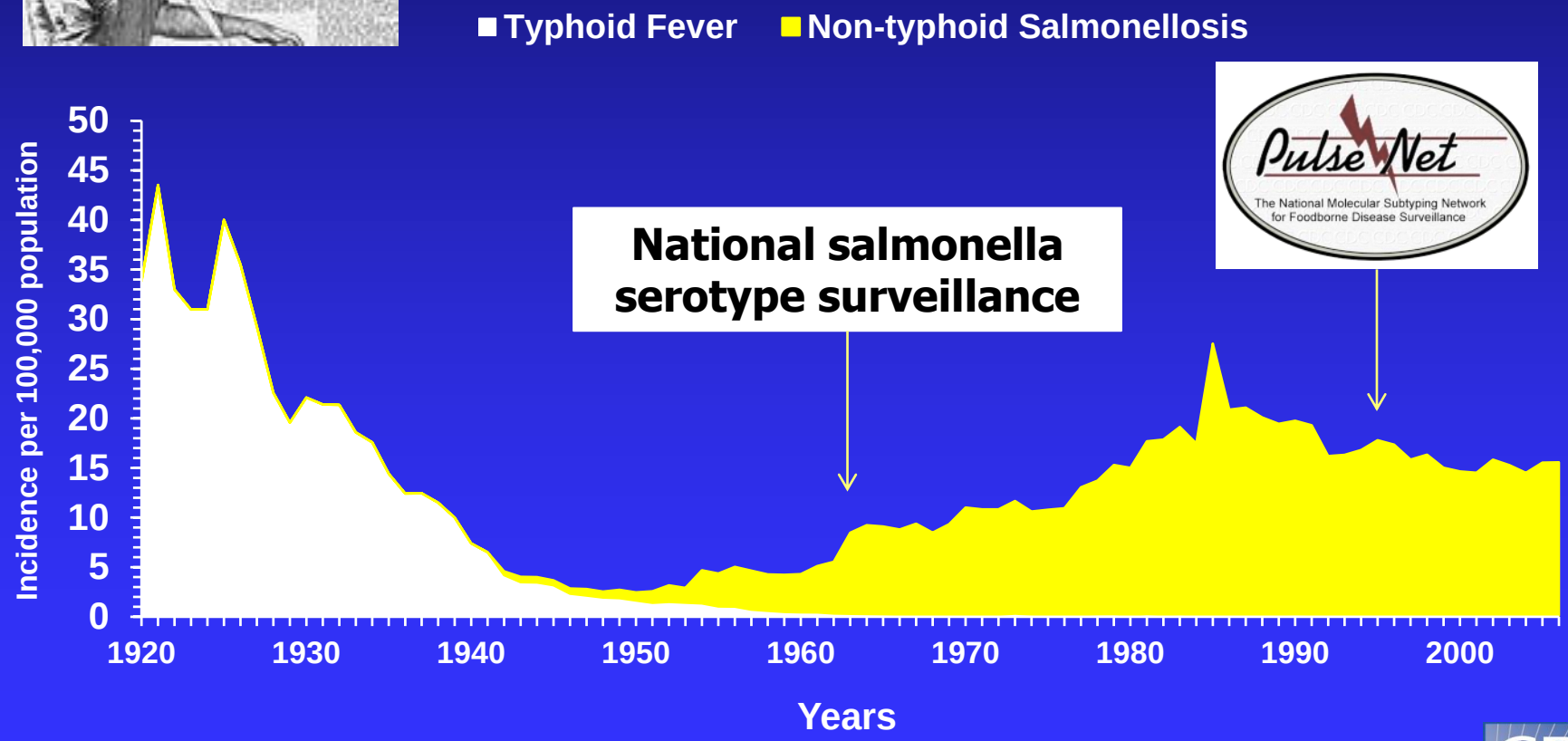
(Note: so is whole genome sequencing, and most other methods being considered)



Companies with Multi-Analyte Gastro Panels in Development

- Luminex xTAG panel (in FDA clearance)
  - Bacteria (10)
  - Viruses (3)
  - Parasites (3)
- Verigene (research use only)
- At least 8 other companies have multi-analyte panels in various stages of development

Nationwide reporting began in 1912
Reported *Salmonella* infections in the United States, 1920-2006



CDC, National surveillance data

CDC
Centers for Disease Control and Prevention

General Strategies to Address Issue

- Short-term: Preserve isolates
- Longer-term: Develop culture-independent pathogen characterization methods
- Very long-term: exploit paradigm shifting technologies

Reflex Culture

Follow-up culture automatically initiated when positive culture independent-based laboratory test results are observed.

(possible when the specimen collected is compatible with culture)

Short-term: Preserve isolates

- Work with medical industry to make new tests compatible with public health needs
- Consider public health impacts in the device licensure process
- Make reflex culture reimbursable?
- Modify State reportable disease rules
- Develop isolate recovery capacity for PHLs
- Sentinel culture-based surveillance?

Longer-term: Develop culture-independent pathogen characterization methods

- Identify ID/subtype/virulence targets for direct molecular detection and characterization
- Exploit new technologies (metagenomics, single-cell sequencing)

Opportunities

- Faster results (better exposure recall, faster intervention)
- Wider understanding of disease causation

Questions

- How can the public health impact of certain test results be better emphasized as test systems are cleared by FDA?
- Are there ways in which the CLIA program can promote public health recommendations (e.g. supporting CDC guidelines and recommendations)?