The New Gram-Negative Challenge

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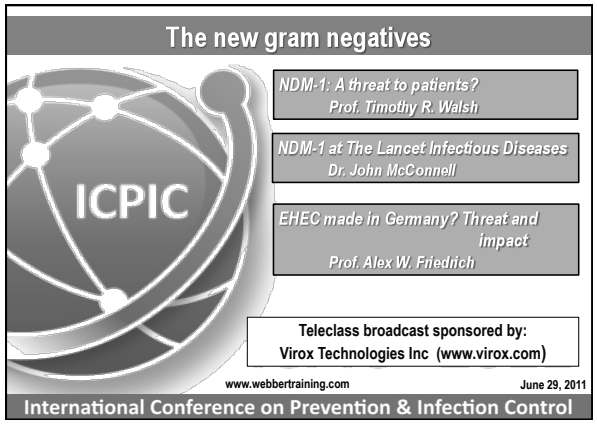

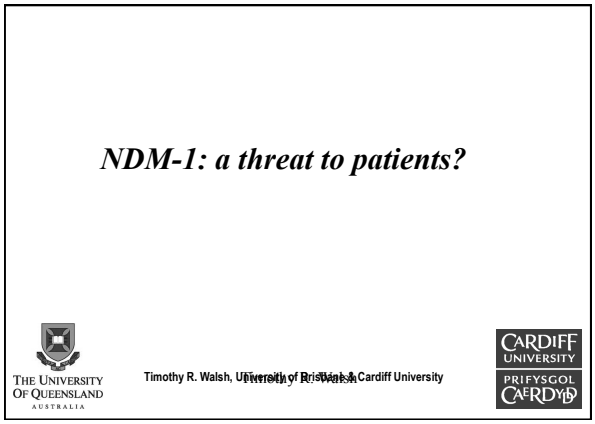

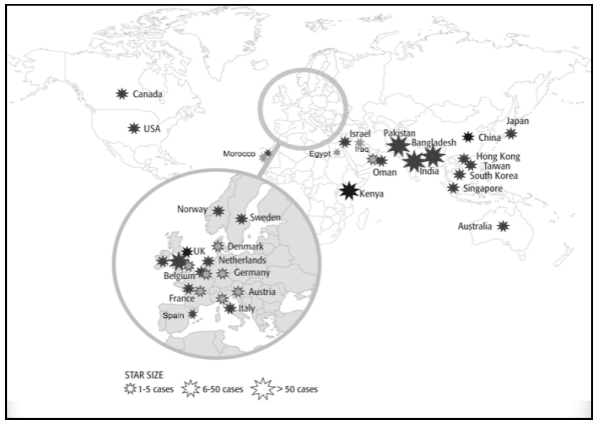

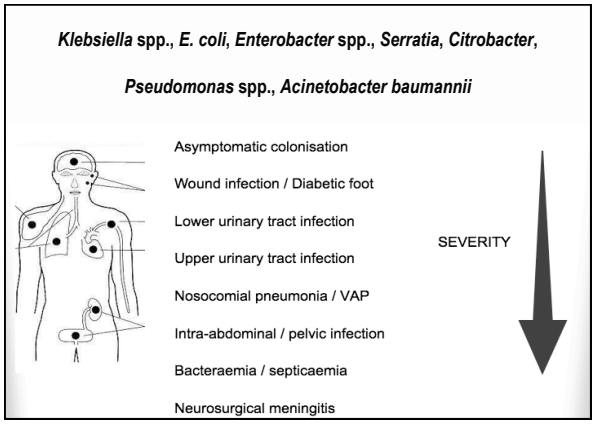

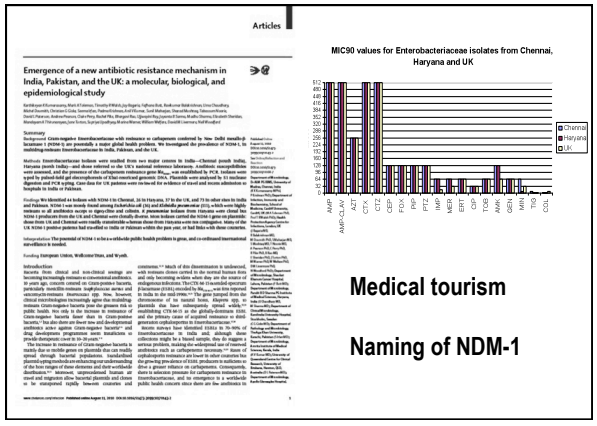

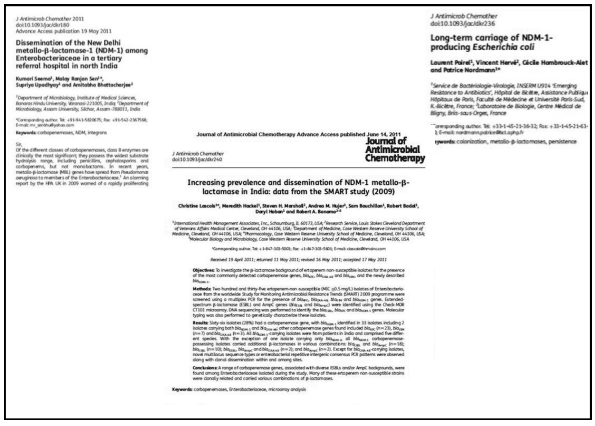

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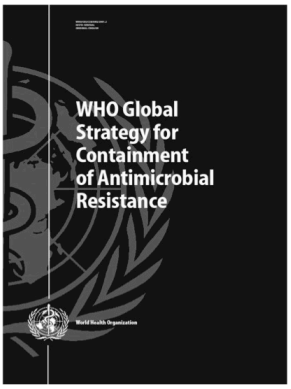
The case of Mr. C

- 40+ yo male
- Visited India at the beginning of 2011 for a religious experience
- Got burnt, dipped in the nearest river
- Admitted to Mumbai Apollo hospital
- Flown to the UK and immediately transported to Bristol
- Amputation and subséquent infections
- NDM-1 positive K. *pneumoniae*, *E. cloacae*, *V. cholera*

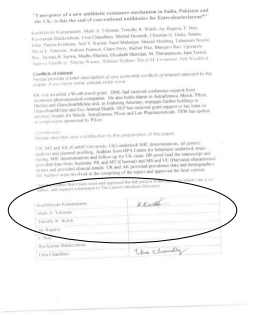


- **Antibiotic Policies**
- **National Surveillance**
- **Encourage International Studies**
- **No link between sanitation and AR resistance**

Witch hunt or responsible journalism?

"HE SAID SOME INTERPRETATIONS WERE WORKED INTO THE REPORT WITHOUT HIS KNOWLEDGE."

SOURCE : THE HINDU 24/8/2010



11tiid0084
Articles
LW

Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study

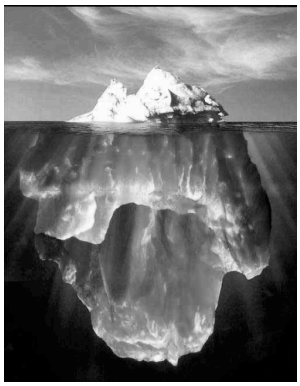
Environmental Study

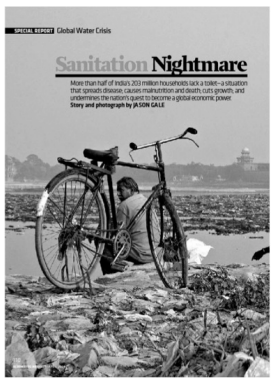
171 swabs
-156 grew meropenem resistant Gram-negatives)
- 51/171 (29.8%) were positive for NDM-1

UNDERESTIMATION!!!

50 water samples
- 14 grew meropenem resistant Gram-negatives)
- 2 out of 50 (4%) were positive for NDM-1

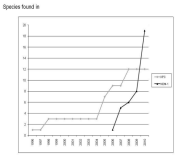
Carriage rates: Pakistan: prevalence of 27.1% in in-patients and 13.8% in out-patients. JAC. Perry et al., 2011. in press

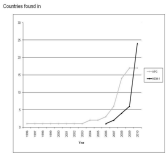




Why is this threat real?

- Only been known for 5 years and has already spread to 28 countries
- Nobody in Southern Asia knows how big the problem is
- The potential for the inter-bacteria transfer is unprecedented
- NDM-1 will inevitably spread to all Gram-negative bacteria
- Pipeline drugs will struggle to cover NDM-1 positive bacteria





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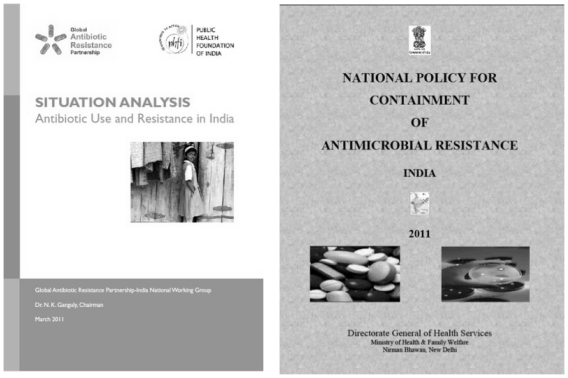

NDM-1: what lessens must we learn?

- Surveillance must be Global or nothing at all
- Science must NOT be politically tainted
- Scientists must be free to work according to their conscience
- National objectives must be in line with the WHO policies on health
- International accountability must be enforced – national audit index based on GDP
- Additional tax to work on infectious diseases

GOOD NEWS DARLING, MY TUMMY TUCK OPERATION HAS BEEN CANCELLED!

THE LANCET

Trusted. Timely. Today's Medicine.

NDM-1 at *The Lancet Infectious Diseases*

ICPIC 2011, Geneva

John McConnell
Editor
The Lancet Infectious Diseases

THE LANCET

THE LANCET

Timeline at *The Lancet*

April 8, 2010: Submitted to *The Lancet*
April 12-15: Fast-track peer review
April 15: Manuscript meeting asks for additional peer review
April 16-19: One more peer reviewer
April 22: Manuscript meeting decides to reject paper

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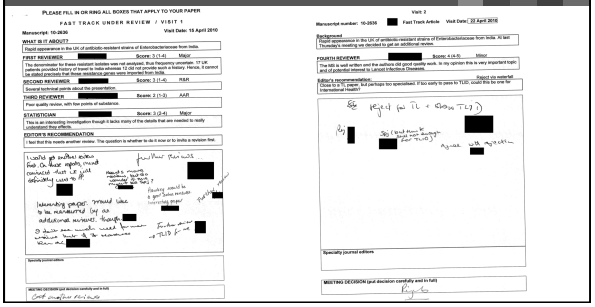
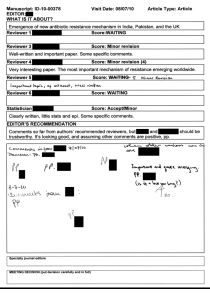


THE LANCET

Timeline at *The Lancet Infectious Diseases*

June 11, 2010: Submitted to *The Lancet Infectious Diseases*
June 14-July 8: Peer review
July 8: Manuscript meeting decides to invite authors to revise the paper
July 13: Revised manuscript submitted
July 20: Paper accepted
August 11: Published online



THE LANCET

Press release sent to about 2000 individuals and agencies worldwide, and posted on press release portals such as EurekAlert (http://www.eurekalert.org/)

THE LANCET

Science Media Centre Round-Up
UNDER EMBARGO UNTIL 00.01am UK TIME WEDNESDAY 11 AUGUST 2010

Expert reaction to new research on drug-resistant bacteria, as published in the *Lancet Infectious Diseases

Professor Richard James, Director of the Centre for Healthcare Associated Infections, University of Nottingham, said:
"This work highlights that C.difficile and MRSA are not the only bacteria that can cause us serious harm. Bacteria that produce extended spectrum beta-lactamases (ESBLs) are resistant to the majority of antibiotics, with the possible exception of the carbapenems; this results in an increased therapeutic use of this class of antibiotics.
Professor Christopher Thomas, Professor of Molecular Genetics, University of Birmingham, said:
"This research illustrates the relentless evolution and spread of antibiotic resistance genes in bacteria which inevitably follows the development and use of new antibiotics in both clinical and community contexts. The rise of infections (eg urinary tract infections) by bacteria that normally are found in the gut (enteric bacteria) but can create severe problems in the old, infirm or those with weakened defences is partly a side product of advances elsewhere in medicine.

Professor Kevin G Kerr, Consultant Microbiologist/Hon Clinical Professor of Microbiology, Harrogate District Hospital, said:
"This investigation highlights the size of the challenge we face in dealing with a new type of resistance in bacteria such as *E. coli* which are common causes of infection both in hospitals and in the community. The number of antibiotics we have left to treat these superbugs is rapidly diminishing and it is conceivable that we will soon see infections which are effectively untreatable. This report shows that the battle to control the emergence of antibiotic resistant superbugs through appropriate use of antibiotics must be fought at an international level."

THE LANCET

Lancet Press Officer email morning of August 11
"TLID antibiotic resistance has been covered pretty much everywhere and calls continue to come in."
BBC Breakfast news (with correct TLID credit) (David Livermore from HPA interviewed, with
Today Programme http://news.bbc.co.uk/today/hi/listen_again/default.stm (0712) (credited throughout programme but not at every point)
BBC Online http://www.bbc.co.uk/news/health-10925411
Plus BBC Q & A: http://www.bbc.co.uk/news/health-10930031
Front page of Guardian http://www.bbc.co.uk/news/health-10925411
And Telegraph- but only small story with no TLID credit. Full Telegraph story Online: http://www.telegraph.co.uk/health/healthnews/7936467/New-superbug-could-make-antibiotics-redundant.html
Daily Mail http://www.dailymail.co.uk/health/article-1302035/Alert-unbeatable-superbug-spread-worldwide.html
Reuters: http://www.reuters.com/article/idUSTRE67A0YU20100811
Bloomberg: http://www.bloomberg.com/news/2010-08-10/drug-resistant-germs-in-india-spreading-to-west-scientists-say.html
Daily Mirror: http://www.mirror.co.uk/news/top-stories/2010/08/11/unstoppable-bug-to-spread-worldwide-115875-22479598/
ABC News: http://abcnews.go.com/Technology/wireStory?id=11372377
Sun: http://www.thesun.co.uk/sol/homepage/woman/health/health/3090188/The-germinator-Invincible-superbugs-from-India-invade-UK.html

August 12: About 240 news stories worldwide, according to Meltwater, an online press "cuttings" service
August 13: 175 stories
August 16: 290 stories

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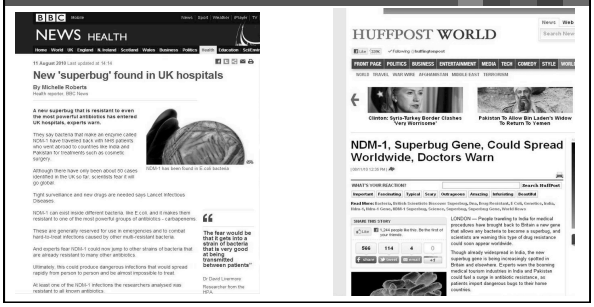

THE LANCET

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THE LANCET

- **Conspiracy to damage medical tourism:**

"What's bugging India is that it is stinking of a conspiracy. A Conspiracy that could damage India's flourishing medical tourism that attract thousands of patients from the west."

- **Sponsorship:**

"Questions are now being raised about why the research was sponsored by two big pharmaceutical companies that may gain from the findings?"

- **"Bad" science, naming controversy:**

"Moreover, the Indian Health Ministry says the research is not supported by scientific data and has rubbished the conclusions. Also, furious about the bacteria named after the capital of the country, India is only reiterating the conspiracy theory."

- **Indian authors dissociating themselves from paper:**

"But reports now suggest the Chennai-based author Karthikeyan Kumarasamy . . . has dissociated himself from parts of it."

THE LANCET

From the Elsevier India office, August 13, 2010

"Yesterday, 12th August there was a front page article published in newspapers in India on a new antibiotic resistant bug. This has generated a huge amount of controversy including getting coverage on TV and being hotly debated in Parliament.

One of the Indian authors has also washed their hands off the last parts of the article alleging that it has been "doctored". It is also being blamed on pharma sponsored research.

The biggest issue is that the article discourages people from coming to India for medical treatment and this is being viewed very negatively. The name of the bug to be NEW DELHI Metalo 1 is seen as extremely negative by all government stakeholders. Dr … whom some of you met in Delhi in April was also on TV criticizing this.

We will need help on the PR front. Needless to say, this is a not going to be a positive development for Elsevier in India in the short term."

THE LANCET

My reply on afternoon of August 13, 2010

- **The journal has signed statements from all authors approving contents of paper.**
- **Clarified involvement of funding sources—ie, no role in writing paper—and that potential conflicts of interest—ie, very few—were clearly stated in the article.**
- **Noted that the name NDM-1 had been published several times before appearing in *The Lancet Infectious Diseases*, and that the evidence for NDM-1 originating in India was very strong.**
- **Suggested Elsevier should steer clear of the controversy.**

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Journal of the Association of Physicians of India, March 2010

"We sought to identify NDM-1 positive strains among the carbapenem resistant Enterobacteriaceae isolates at our tertiary care centre [in Mumbai]. In a short span of 3 months, we identified 22 such organisms… The identification of NDM-1 in 22 of 24 isolates is a worrisome development indeed. NDM-1 being present among Enterobacteriaceae has the potential for further dissemination in the community. Such dissemination may endanger patients undergoing major treatment at centres in India and this may have adverse implications for medical tourism."

THE LANCET

Journal of the Association of Physicians of India, March 2010

"Our country, India, is the world leader in antibiotic resistance, in no other country [are] antibiotics been misused to such an extent . . . Whatever weapons we had in the form of antibiotics, we ourselves have ruined them. Indian medical community has to be ashamed of the NDM-1 ("New Delhi Metallo-1") gene. Even though we have not contributed to carbapenem development, we have contributed a resistance gene with a glamorous name. The overuse of antibiotics is embedded in our Indian gene. It is an Indian tradition."

THE LANCET

Indian Journal of Medical Microbiology, July 17, 2010

"New Delhi metallo-beta-lactamases (NDM) is a nomenclature that Indians cannot be proud of . . . The virtual nonexistence of antibiotic policies and guidelines in India ... is a major driver of the emergence and spread of multidrug resistance in India. This is augmented by the unethical and irresponsible marketing practices of the pharmaceutical industry, and encouraged by the silence and apathy of the regulating authorities. Poor microbiology services in most parts of the country add to the problem."

THE LANCET

Comment letters, published November, December 2010

•About 30 received, more than on any other paper published by TLID.
• 7 published November, all but one with Indian authors, plus reply from Walsh and colleagues.
Themes:
Clinical significance, patient confidentiality, naming, medical tourism and origin in India, clonal lineages, is NDM-1 "just" another carbapenemase?, Indian strategies for combating antibiotic resistance.
• 6 published December, describing spread of NDM-1 to Singapore, Germany, Denmark, Netherlands, Belgium, and France.

THE LANCET

Lancet won't publish India's rebuttal

British medical journal *The Lancet* have refused to publish India's rebuttal in connection with an article in which a drug-resistant superbug was named after New Delhi.

The National Centre for Disease Control (NCDC), in the rebuttal, disagreed with the naming of the bacteria as New Delhi Metallo-Beta-lactamase-1. However, *Lancet* Editor Richard Horton, while on a visit to India later, apologised for the naming.

Responding to the rebuttal, Editor of *Lancet Infectious Diseases* John McConnel sent a letter to the then Director of NCDC, R.L. Ichhpujani, refusing to publish the document, saying the journal had received far more submissions than it had the space to publish.

Mr. McConnel's letter said:

"Thank you for submitting your manuscript to the *Lancet Infectious Diseases*. The Journal's editors have discussed the manuscript and our decision is that it would be better placed elsewhere. We currently receive far more submissions than we have space to publish and, therefore, have to reject many otherwise worthy papers.

"We are sorry we cannot be more helpful on this occasion, and we hope you will think of us again in the future."

The letter was dated November 2, 2010.

THE LANCET

India today came out out strongly against a report on presence of a drug resistant bacteria in the public water system of the capital saying the reviews behind it were not "scientific" and the government will respond in an appropriate forum.

"Just to keep the heat on a country or a region ... is not scientific motive for a study," Secretary Department of Health Research V V Kalkoni told reporters here.

"Enough is enough, scientifically we will respond to it in an appropriate forum," Kalkoni, who is also the Director of Indian Council of Medical research said.

International medical journal Lancet reported that deadly superbug NDM-1 was found in about a quarter of water samples taken from drinking supplies and puddles on the streets of New Delhi.

He said that the report was unsupported by any "clinical and epidemiological" evidence and also does not highlight the "unstable character of the isolates".

Quoting from a study conducted by microbiologists of the Ganga Ram Hospital, Shashi Khare, Deputy Director National Centre for Disease Control, said, out of 1, 042 pregnant women screened, none had the New Delhi metallo-1 resistance which should be present if a person is carrying NDM-1 bacteria in their gut.

The study was carried out over the last two years. The research shows that E Coli isolated from the gut of a large randomly selected sample of pregnant women did not show any carbapenem resistant E Coli in the stool samples indicating no presence of NDM1, Khare said.

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THE LANCET

http://www.changesuperbugname.com/ 10138 signatories

THE LANCET

A good experience?

- Expect microbiology to throw up the unexpected
- Pleased that TLID could offer a natural home to such an important paper after *Lancet* rejection
- Reaction to the paper was unpredictable, with government seeming less well informed than media
- Science is not free of political and cultural context
- The environment within which research is done can be hostile to uncomfortable news
- It's good to start with a bang!

EHEC made in Germany? threat and impact

Alex W. Friedrich

Chair of Medical Microbiology and Infection Control

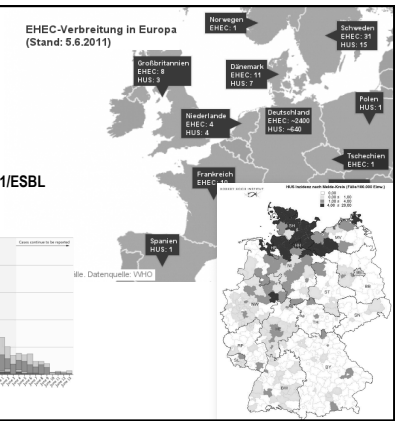
University Medical Centre Groningen (NL)

What is EHEC?

EHEC O104:H4 outbreak In Germany

- 3222 cases
- 810 HUS
- 39 patients died

- E. coli O104:H4 HUSEC41/ESBL



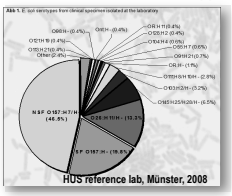
Frank et al. 2011 N Engl J Med

Shiga Toxin-producing (STEC) and Enterohemorrhagic *Escherichia coli* (EHEC)

Symptomatic

- Diarrhea
- Bloody Diarrhea
- Haemolytic-Uraemic Syndrome (HUS)
  - Acute renal failure
- Neurological symptoms

Usual HUS-associated Serotypes



High priority for public health

- HUS (most frequent cause for acute renal failure)
- Large outbreaks (1997 Japan: 11.000, 2002 USA: 2500, 2004 Ger: 250)
- No specific therapy
- No specific prevention (e.g. vaccination)

Mellmann *et al.*, Clin. Infect. Dis. 2005
Friedrich *et al.*, Clin. Infect. Dis. 2007

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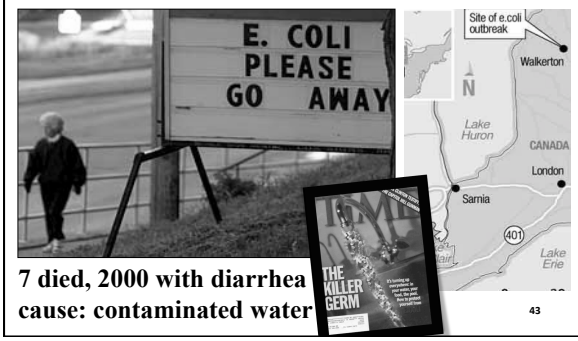
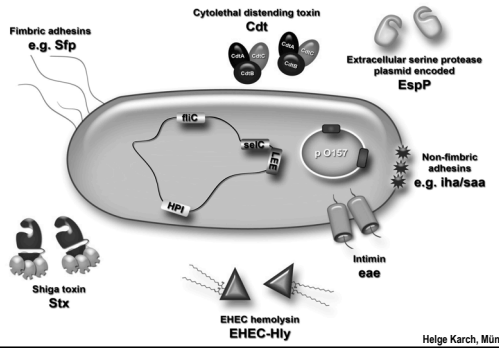
EHEC O157:H7 outbreak in Canada



7 died, 2000 with diarrhea
cause: contaminated water

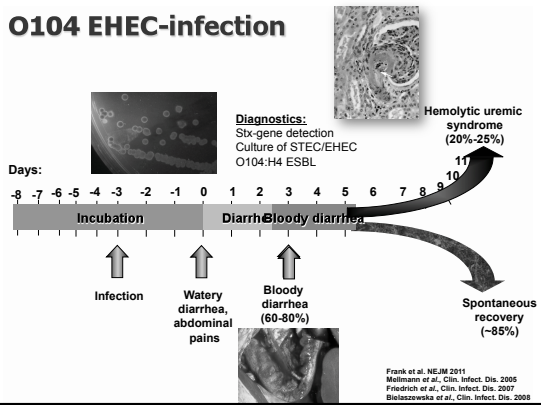
43

The toxin cocktail of classical EHEC O157



Helge Karch, Münster

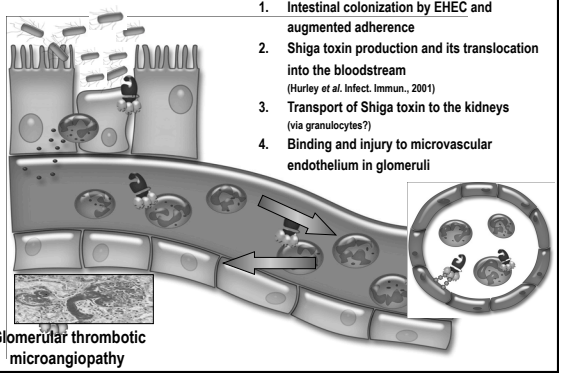
O104 EHEC-infection



Frank et al. NEJM 2011
Mellmann *et al.*, Clin. Infect. Dis. 2005
Friedrich *et al.*, Clin. Infect. Dis. 2007
Bielaszewska *et al.*, Clin. Infect. Dis. 2008

Hemolytic uremic syndrome: Pathogenesis

1. Intestinal colonization by EHEC and augmented adherence
2. Shiga toxin production and its translocation into the bloodstream
   (Hurley *et al.* Infect. Immun., 2001)
3. Transport of Shiga toxin to the kidneys
   (via granulocytes?)
4. Binding and injury to microvascular endothelium in glomeruli

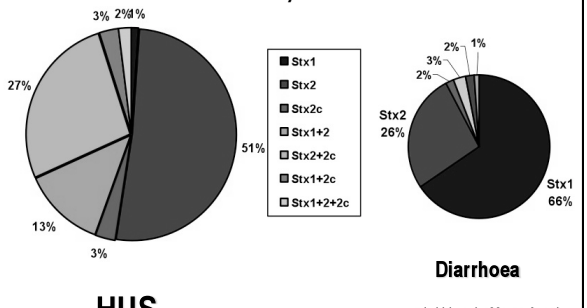


Glomerular thrombotic microangiopathy

What is different than before?

Data of National Reference lab for HUS 2001-2010	German EHEC outbreak (Frank et al. NEJM)
• n= 812	• n> 810
• Children: <5y	• **Adults**: 49 (22-87); Children (11, 4-15)
• EHEC O157, O26, O103, O111, O145	• EHEC **O104:H4/ESBL**
• Incubation period diarrhea 3d	• Incubation period diarrhea **8d**
• Incubation period HUS +7d	• Incubation period HUS **+5d**
• bloody diarrhea:60%	• bloody diarrhea:**83%**
• HUS in 15%	• HUS in **20%-25%**
• Neorological symptoms: 25%	• Neorological symptoms: **35%**

Shiga Toxin-Variants remain a good predictor for the severity of disease



Friedrich et al. 2002. J Infect Dis.
Friedrich et al. 2003. J Clin Micro.
Friedrich et al. 2009 Clin Infect Dis.

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Is it a new strain…?

O104:H4

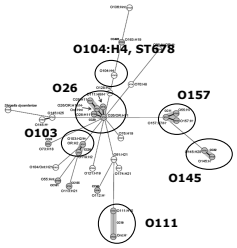
HUSEC41, firstly identified in Germany 2001 in two sibblings

MLST ST 678

Stx2+, stx1-, eae-, hly-

Sorbitol-fermenting+

Tellurite-resistant



A. Mellmann *et al.*, Emerg Infect Dis 2008, 14 (8): 1287-1290

….not really!

O104:H4

Mostly similar to reference strain HUSEC41

typical *EAEC loci* (*aggA, aggR, set1, pic, aap*)

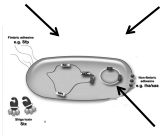
typical EHEC loci (*stx2, iha, lpfO26, lpfO113*)

92% EAEC+stx2a+iha

Stack-bricked „aggregative adherence"

Other fimbriae and no EAST-1

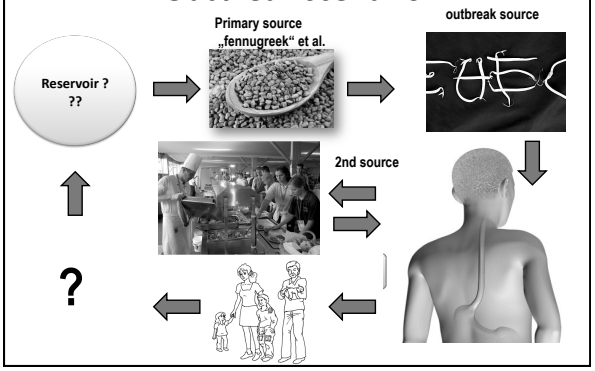
No ETEC, EPEC or EIEC typical loci



ESBL (CTX-M, TEM)

Bielaszewska et al. Lancet Infect Dis. 2011

Outbreak scenario



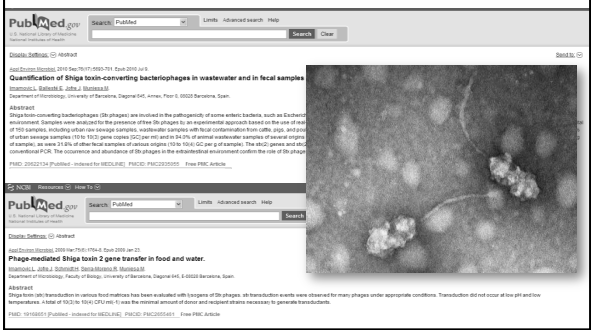
EHEC on fruits and veg

1997	*E. coli* O157:H7	Sprouted seeds (alfalfa)	Sivaplasingham *et al.* 2004
1997	*E. coli* O157:H7	Salad	Anon (2005a)
1998	*E. coli* O157:H7	Salad	Anon (2001a,b)
1998	*E. coli* O157:H7	Fruit salad	Anon (2001a,b)
1998	*E. coli* O157:H7	Coleslaw	Anon (2001a,b)
1998	*E. coli* O157:H7	Sprouted seeds (clover/alfalfa)	Taormina *et al.* 1999
1998	*E. coli* O157:H7	Unpasteurized apple juice	Anon (2001a,b)
1998	*E. coli* O157:H7	Parsley	Sivaplasingham *et al.* 2004
1999	*E. coli* O157:H7	Coriander (cilantro)	Campbell *et al.* 2001
1999	*E. coli* O157:H7	Unpasteurized apple juice	Anon (2001a,b)
2003	*E. coli* O157:H7	Cucumber	Duffell *et al.* (2003)
2003	*E. coli* O157:H7	Lettuce	Anon (2005a)
2005	*E. coli* O157:H7	Lettuce	Söderström *et al.* (2005)
2006	*E. coli* O157:H7	Spinach	CDC (2006b)
2006	*E. coli* O157:H7	Lettuce	CDC (2006c)

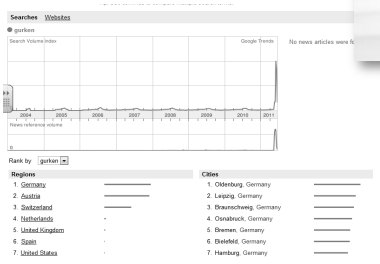
Pathogen	Environment	Survival (day)	References
Escherichia coli O157:H7	Soil + animal manure	30	Nicholson *et al.* (2005)
E. coli O157:H7	Soil + animal manure	99	Nicholson *et al.* (2005)
E. coli O157:H7	Animal manure	60	Avery *et al.* (2005)
E. coli O157:H7	Slurries	60	Avery *et al.* (2005)
E. coli O157:H7	Abattoir waste	60	Avery et al. (2005)
E. coli O157:H7	Sewage sludge	60	Avery et al. (2005)
E. coli O157:H7	Nonaerated ovine manure	>365	Kudva *et al.* (1998)
E. coli O157:H7	Aerated ovine manure	120	Kudva *et al.* (1998)
E. coli O157:H7	Nonaerated slurry	600	Kudva *et al.* (1998)
E. coli O157:H7	Aerated slurry	30	Kudva *et al.* (1998)
E. coli	Slurry + dirty water	90	Nicholson *et al.* (2005)

Heaton and Jones, J Appl Microbiol 2007

Stx-genes: common in nature



This time Innocent



A Webber Training Teleclass
www.webbertraining.com

The New Gram-Negative Challenge

Broadcast live from the International Conference on Prevention and Infection Control

Teleclass broadcast sponsored by Virox Technologies Inc (www.virox.com)

From point source to human-to-human…

- Major point source (fennugreek sprouts from Bienenbüttel)
  - but where do the seeds come from ????
- O104:H4 EHEC (1)/ HUS (7) in 8 adult patients (6 woman) in France (seeds from UK or elsewhere?)
- 3 children (2 HUS) in school in Northwest Germany (3 persons in school kitchen asymptomatic and EHEC-positive)
- RKI-Sentinel of bloody diarrhea at hospital admission is still elevated in outbreak regions

Cholera outbreak in Hamburg, 19th century

Preventive Microbiology & Hygiene:

An new old concept


Vibrio cholerae,


Hamburger Gängeviertel 1892


Robert Koch

Cholera-infection control measures (1908):

„Everything depends on the fact that we have valid detection methods for the microorganisms.

This counts especially for the human carrries who contribute most for the spread of the disease"

Speech of Robert Koch on 11.2.1908 in front of the Medical Order of Berlin
Deutsche Medizinische Wochenschrift, 1908, Nr. 8

O104:H4 – A new Chapter

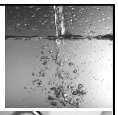
Changed HUSEC41 comeback: It's an EHEC

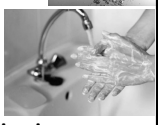
Enhanced Pathogenicity
- EHEC HUS in adults (woman?)
- High CMI = low antibody prevalence in population?

Newly acquired Resistance
- First time ESBL-resistance in obligatory pathogen with no specific therapy
- CTX-M-15 resistance known in humans

Different Epidemiology
- Longer incubation period
- EAEC is known for its human reservoir
- Diarrheagenic pathogen with severe complication
- Asymptomatic carriers and spreaders!

Action now!

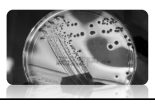




- Find the **reservoir**: Our Food and water must be safe!
- **Personal hygiene** is crucial – Diarrea is not normal !
- **Those who call for central coordinated action in Germany, should also call for central coordinated action in Europe**
- **Focus on Communication and early detection!**
- **Germany has done maximum effort, nobody would have been really prepared for this.**

Are we all prepared now?

- Veterinay and human medicine must work together (One-Health)
- Need for international, basic and applied research
- Foster Preventive Microbiology & Infection Protection!



Thank you!

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