


# 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)



**The new gram negatives**

*NDM-1: A threat to patients?*  
Prof. Timothy R. Walsh

*NDM-1 at The Lancet Infectious Diseases*  
Dr. John McConnell


*EHEC made in Germany? Threat and impact*  
Prof. Alex W. Friedrich

Teleclass broadcast sponsored by:  
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www.webbertraining.com June 29, 2011

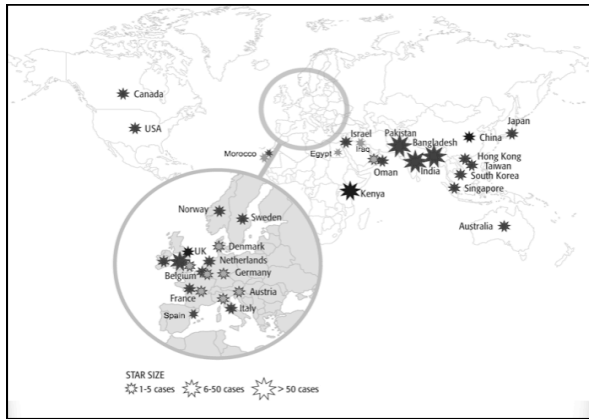
**International Conference on Prevention & Infection Control**

## NDM-1: a threat to patients?

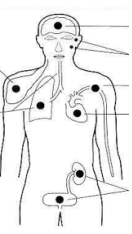


Timothy R. Walsh, **University of Queensland, Cardiff University**






***Klebsiella* spp., *E. coli*, *Enterobacter* spp., *Serratia*, *Citrobacter*,  
*Pseudomonas* spp., *Acinetobacter baumannii***



- Asymptomatic colonisation
- Wound infection / Diabetic foot
- Lower urinary tract infection
- Upper urinary tract infection
- Nosocomial pneumonia / VAP
- Intra-abdominal / pelvic infection
- Bacteraemia / septicaemia
- Neurosurgical meningitis

SEVERITY



Articles

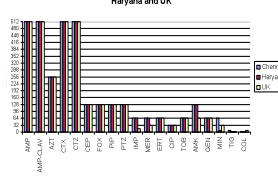
### Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study

**Journal of Antimicrobial Chemotherapy** 66:1233-1241 (2011)

**Keywords:** NDM-1, beta-lactamase, India, Pakistan, UK, antibiotic resistance, epidemiology.

**Summary:** A novel class of beta-lactamase, NDM-1, was first identified in India in 2005. It is a metallo-beta-lactamase that hydrolyzes all beta-lactams, including carbapenems. NDM-1 is now widespread in India, Pakistan, and the UK. This study investigated the molecular biology and epidemiology of NDM-1.

### MIC50 values for Enterobacteriaceae isolates from Chennai, Haryana and UK



The chart compares MIC50 values for 12 antibiotics: AMO-CLAV, AZT, CFT, CEF, FOX, PFT, AMP, MER, CIP, TOB, AMK, and TOF. MIC50 values are shown in mg/L on a logarithmic scale from 0.001 to 1000.000.

**Medical tourism**

**Naming of NDM-1**

### Dissemination of the New Delhi metallo-beta-lactamase-1 (NDM-1) among Enterobacteriaceae in a tertiary referral hospital in north India

**Journal of Antimicrobial Chemotherapy** 66:1203-1208 (2011)

**Keywords:** NDM-1, Enterobacteriaceae, tertiary referral hospital, India.

**Summary:** A study of 100 Enterobacteriaceae isolates from a tertiary referral hospital in north India. NDM-1 was detected in 15% of isolates. The study investigated the dissemination of NDM-1 among these isolates.

### Long-term carriage of NDM-1-producing Escherichia coli

**Journal of Antimicrobial Chemotherapy** 66:1213-1218 (2011)

**Keywords:** NDM-1, Escherichia coli, long-term carriage.

**Summary:** A study of long-term carriage of NDM-1-producing E. coli in patients. The study found that NDM-1 carriage persisted for several months in patients.

**Increasing prevalence and dissemination of NDM-1 metallo-beta-lactamase in India: data from the SMART study (2009)**

**Journal of Antimicrobial Chemotherapy** 66:1219-1224 (2011)

**Keywords:** NDM-1, SMART study, India, prevalence, dissemination.

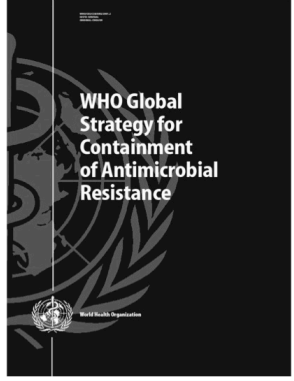
**Summary:** Data from the SMART study showing the increasing prevalence and dissemination of NDM-1 in India from 2009 to 2010.

# The New Gram-Negative Challenge

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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 subsequent 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?*

by SHEKHAR GUPTA

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

SOURCE : THE HINDU 24/8/2010

111610084  
Articles  
LW

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

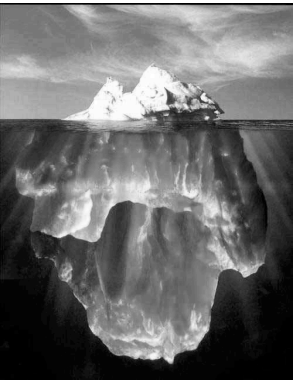
**Environmental Study**


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





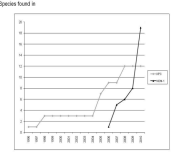
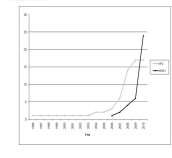
**Sanitation Nightmare**

More than half of India's 103 million households lack a toilet - a situation that spreads disease, causes malnutrition and death, cuts growth, and undermines the nation's quest to become the global economic power.

Story and photograph by JASON GALE

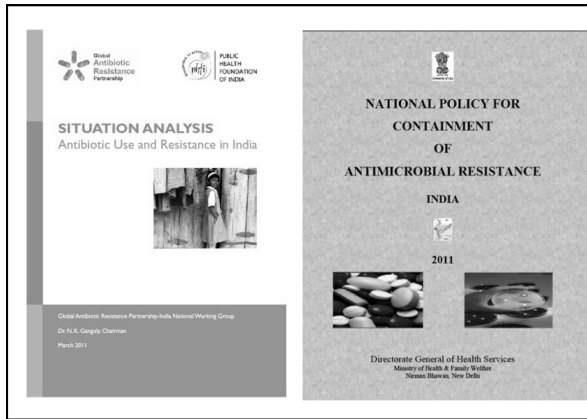
*Why is this threat real?*

- 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 lessons 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



THE LANCET

Trusted. Timely. Today's Medicine.

**NDM-1 at *The Lancet Infectious Diseases***  
ICPIC 2011, Geneva

John McConnell  
Editor  
*The Lancet Infectious Diseases*



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**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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PLEASE FILL IN THE BOXES WHICH APPLY TO YOUR PAPER

**FAST TRACK UNDER REVIEW / VISIT 1**      Visit Date: 13 April 2010

Manuscript ID: 10-0558      Article Type: Fast Track Article      Visit Date: 13 April 2010

**POINT OF CONTACT:** [Redacted] Email: [Redacted]

**TITLE:** [Redacted]

**ABSTRACT:** [Redacted]

**KEY WORDS:** [Redacted]

**INTRODUCTION:** [Redacted]

**CONCLUSION:** [Redacted]

**REFERENCES:** [Redacted]

**ACKNOWLEDGEMENTS:** [Redacted]

**DECLARATION OF INTEREST:** [Redacted]

**FOOTNOTES:** [Redacted]

**REFERENCES:** [Redacted]

**ACKNOWLEDGEMENTS:** [Redacted]

**DECLARATION OF INTEREST:** [Redacted]

**FOOTNOTES:** [Redacted]

**THE LANCET**

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## Timeline at *The Lancet Infectious Diseases*

**June 11, 2010: Submitted to *The Lancet Infectious Diseases***  
**June 14-15, 2010: 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**

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### THE LANCET INFECTIOUS DISEASES: Press Release

INTERNATIONAL TRAVEL INCREASING SPREAD OF NEW DRUG-RESISTANT BACTERIA: IS THIS THE END OF ANTIBIOTICS?

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

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### 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 *CdfricIII* and *Mrsa* are not the only bacteria that can cause 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."

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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/1/hi/health/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.guardian.co.uk/health/2010/aug/10/antibiotics-resistance>  
 Ant Telegraph - but only small story with no TLID credit. Full Telegraph story Online: <http://www.telegraph.co.uk/health/healthnews/2336467/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/idUS1RE67AYU1010081>  
 Bloomberg: <http://www.bloomberg.com/news/2010-08-10drug-resistant-germs-in-bug-spread-to-west-scientists-say.html>  
 Daily Mirror: <http://www.mirror.co.uk/news/top-stories/2010/08/11/unstoppable-bug-to-spread-worldwide-115675-2473898>  
 ABC News: <http://abcnews.go.com/Technology/wireStory?id=11372377>  
 Sun: <http://www.thesun.co.uk/sol/homepage/health/health3090188/>  
 The-germator-invincible-superbugs-from-india-invoke-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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### New 'superbug' found in UK hospitals

By Michelle Rowland  
Health reporter, BBC News

A new antibiotic fight is expected to start as the most powerful antibiotic has returned to UK hospitals, reports a new study.

This key discovery has been made as researchers from the University of Liverpool, UK, have shown that the most powerful antibiotic has returned to UK hospitals, reports a new study.

Although the bug has only been found in UK hospitals, it is not the first time that the bug has been found in the UK.

Tight surveillance and new drugs are needed says Lancet Infectious Diseases

NDM-1 can resist most different antibiotics, but it is also resistant to those that are used to treat most common infections.

There are currently no drugs to treat infections caused by this most powerful bacteria.

And reports that NDM-1 could be used to treat other strains of bacteria that are already resistant to other antibiotics.

However, the study provides reassurance that most superbugs do not spread rapidly from person to person and are almost impossible to treat.

Although the NDM-1 is linked to the researchers involved, it is not related to all other antibiotics.

### NDM-1, Superbug Gene, Could Spread Worldwide, Doctors Warn

By Bruce Rapley  
Senior Staff Writer

Doctors warn that a new gene that makes bacteria resistant to antibiotics could spread worldwide.

NDM-1, a gene that makes bacteria resistant to antibiotics, could spread worldwide, doctors warn.

The gene, which is found in bacteria from India, is called NDM-1. It is a type of gene that makes bacteria resistant to antibiotics.

Doctors warn that the gene could spread worldwide, making it difficult to treat infections.

The gene is found in bacteria from India, and it is called NDM-1. It is a type of gene that makes bacteria resistant to antibiotics.

Doctors warn that the gene could spread worldwide, making it difficult to treat infections.

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### India rejects UK scientists' 'superbug' claim

By Bruce Rapley  
Senior Staff Writer

India has rejected a claim by British scientists that a new superbug, named after New Delhi, has emerged in the UK.

The new superbug, named after New Delhi, has emerged in the UK. It is called NDM-1.

India has rejected the claim that the superbug was spread from India to the UK.

The superbug is called NDM-1. It is a type of gene that makes bacteria resistant to antibiotics.

Doctors warn that the gene could spread worldwide, making it difficult to treat infections.

### Super-bug named after New Delhi bugs India

NDTV Correspondent  
Updated August 13, 2010 12:14:37

Super-bug named after New Delhi bugs India

The superbug is called NDM-1. It is a type of gene that makes bacteria resistant to antibiotics.

Doctors warn that the gene could spread worldwide, making it difficult to treat infections.

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### Super-bugged, Govt trashes study by own scientists

By Anand Bhatnagar  
Senior Reporter

The government has trashed a study by its own scientists that claimed to have found a new superbug in India.

The study, which was published in The Lancet, claimed to have found a new superbug in India.

The government has trashed the study, saying it was not supported by scientific data.

The study was published in The Lancet. It claimed to have found a new superbug in India.

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### India trashes 'superbug' report, says it's doctored

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India has trashed a report by its own scientists that claimed to have found a new superbug in India.

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- 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."

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### From the Elsevier India office, August 13, 2010

"Yesterday, 12<sup>th</sup> 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 Metallo 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."

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### 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**

**New Delhi Metallo- $\beta$ -lactamase (NDM-1) in Enterobacteriaceae: Treatment options with Carbapenems Compromised**

**Abstract**

**Objective:** 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.

**Introduction**

Carbapenems are the most potent class of antimicrobials available. They are used for the treatment of severe infections caused by Gram-negative bacteria. The emergence of carbapenem resistance in Gram-negative bacteria is a major public health concern. 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.

**Methods and Results**

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.

**Conclusion**

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.

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**Journal of the Association of Physicians of India, March 2010**

**An obituary: On the Death of antibiotic**

**Abstract**

Our country, India, is the world leader in antibiotic resistance, in no other country [are] antibiotics being 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- $\beta$ -lactamase") 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.

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**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."**

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**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.

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**THE HINDU**

HEALTH - POLICY & ISSUES

NEW DELHI, April 15, 2011

**Lancet won't publish India's rebuttal**

**SPECIAL CORRESPONDENT**

**RELATED**

British medical journal The Lancet has 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 - Boverius; General Editor Richard Horton, who was a critic in India, says, spokesman for the journal.

Responding to the rebuttal, Editor of Lancet Infectious Diseases Ashis DasGupta wrote a letter to the then Director of NCDC, H. J. Subhasini, asking to publish the document, saying the journal had received far more submissions than it had the space to publish.

Mr. McCosker's letter said:

"Thank you for submitting your manuscript to the Lancet Infectious Diseases. The journal editors have discussed the manuscript and one decision is that it would be better placed elsewhere. We normally 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

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

**Abstract**

India has been one of the first to report the presence of a drug resistant bacteria in its public water system (the distribution of the bacteria defined it were not "toxic" and the government did not respond in an appropriate form.

"Just to keep the faith of a country or a region. . . . In no scientific method for a study." The study Department of Health Research in a research that replicates this.

"Though it is enough, scientifically we will respond to it in an appropriate form." Kathach, the director of Health Council of India, says.

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

It said that the report was unsupported by any "clinical and epidemiological" evidence and also does not support the "serious character of the matter".

Quoting from a study conducted by microbiologists of the Ganga Nam Trust, Ganga Ghosh, Senior Director National Centre for Disease Control, said, and it's a well prepared review review, some had any Carbapenem resistance which should be present in a person's body. I will be in your gut."

The study was carried out over the last two years. The research shows that E. Coli isolated from the set of a large capacity water supply pipes of progress rates do not show any Carbapenem resistant E. Coli in the 100 samples including the presence of NDM-1.

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Online edition reporting Change of name for HUS Superbug

**New Delhi Superbug**  
 It stigmatizes a city and a nation. Let's change the name.

Sign Online Petition

Your Name, Title & Location\*  
 Country:  State/Province:  Postal Code:   
 Email:   
 Street:   
 City:   
 Country:

I am not a robot. Please don't change my CAPTCHA.

Help your country, spread the news

A request to sign this petition

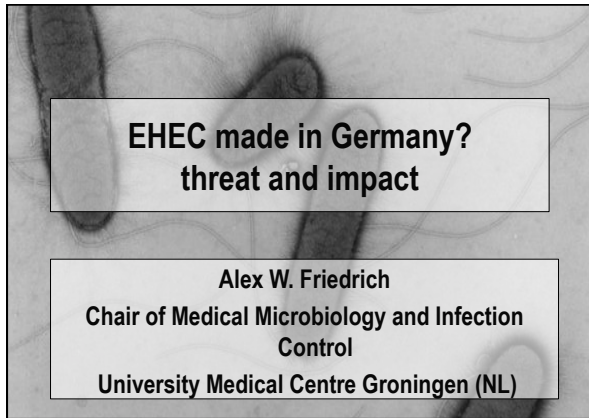
Initiated by Dr. Hans-Joachim Tenckhoff, Infectious Disease physician in Hamburg, GERMANY and India

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

THE LANCET

## A good experience?

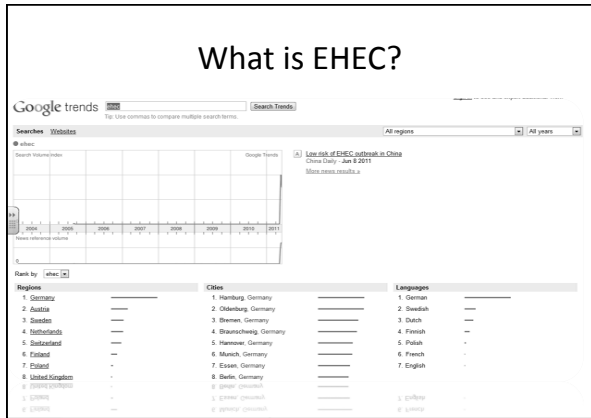
- Expect microbiology to throw up the unexpected
- Pleased that TLID could offer a natural home to such an important paper after Lancet rejection
- Reaction to the paper was unpredictable, with government seeming less well informed than media
- Science is not free of political and cultural context
- 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

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## What is EHEC?



Google Trends

Search: EHEC

Regions: 1. Germany, 2. Sweden, 3. Denmark, 4. Netherlands, 5. Switzerland, 6. Poland, 7. Poland, 8. United Kingdom

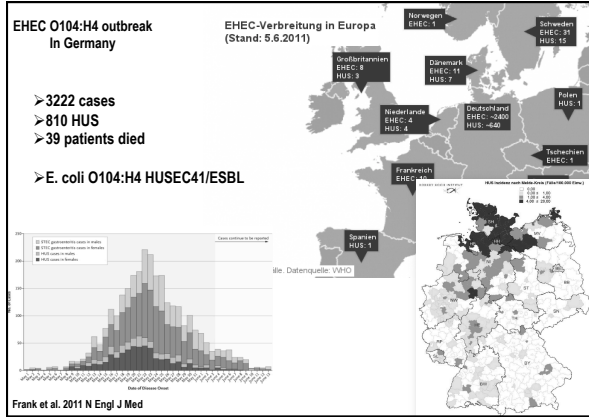
Cities: 1. Hamburg, Germany, 2. Oldenburg, Germany, 3. Bremen, Germany, 4. Braunschweig, Germany, 5. Hannover, Germany, 6. Munich, Germany, 7. Essen, Germany, 8. Berlin, Germany

Languages: 1. German, 2. Swedish, 3. Danish, 4. Finnish, 5. Polish, 6. French, 7. English

## EHEC O104:H4 outbreak in Germany

➢ 3222 cases  
 ➢ 810 HUS  
 ➢ 39 patients died

➢ E. coli O104:H4 HUSEC41/ESBL



EHEC-Verbreitung in Europa (Stand: 5.6.2011)

Norwegen EHEC-1, Schweden EHEC-35 HUS-15, Polen HUS-1, Tschechien EHEC-1, Deutschland EHEC-3205 HUS-620, Dänemark EHEC-11 HUS-7, Niederlande EHEC-4 HUS-4, Frankreich EHEC-1, Spanien HUS-1, Großbritannien EHEC-3 HUS-3

Frank et al. 2011 N Engl J Med

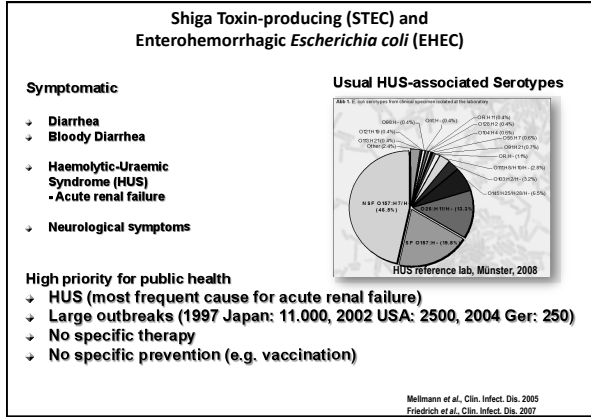
## Shiga Toxin-producing (STEC) and Enterohemorrhagic Escherichia coli (EHEC)

### Symptomatic

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

### 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)



Usual HUS-associated Serotypes

HUS reference lab, Münster, 2008

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

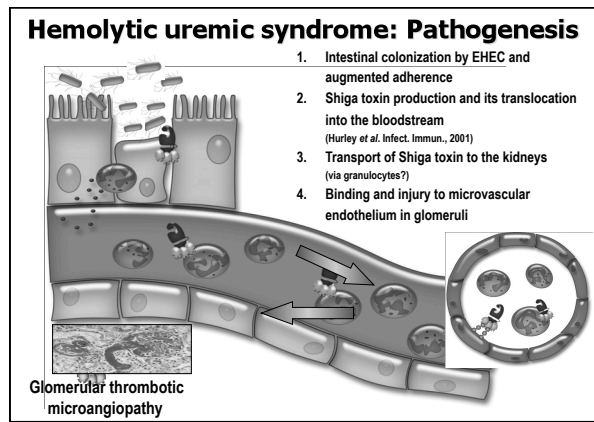
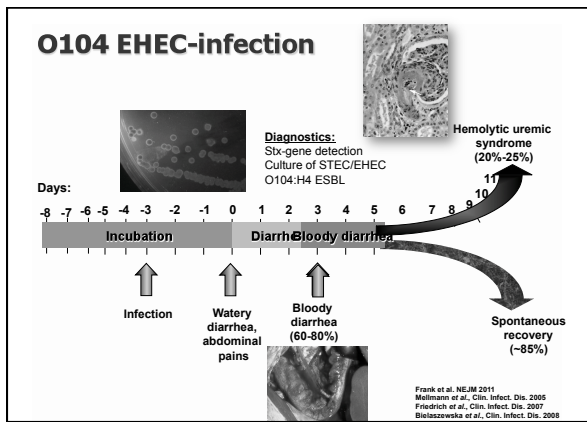
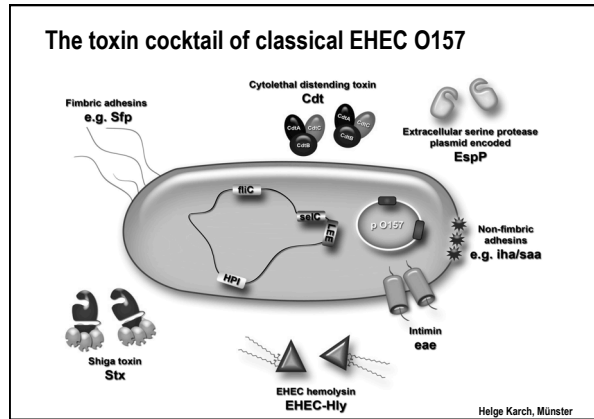
# The New Gram-Negative Challenge

Broadcast live from the International Conference on Prevention and Infection Control  
Teleclass broadcast sponsored by Virox Technologies Inc ([www.virox.com](http://www.virox.com))

**EHEC O157:H7 outbreak in Canada**

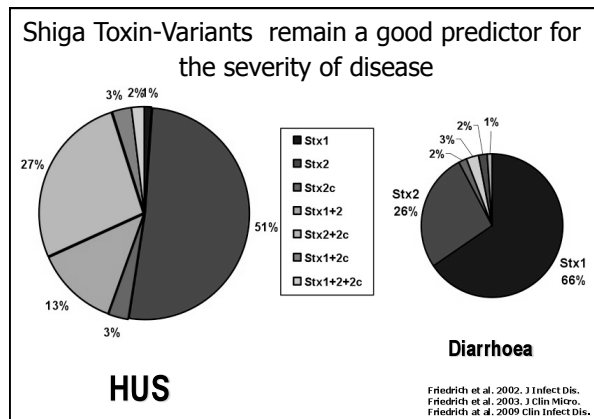
7 died, 2000 with diarrhea  
cause: contaminated water

43



**What is different than before?**

Data of National Reference lab for HUS 2001-2010	German EHEC outbreak (Frank et al. NEJM)
<ul style="list-style-type: none"> <li>n= 812</li> <li>Children: &lt;5y</li> <li>EHEC O157, O26, O103, O111, O145</li> <li>Incubation period diarrhea 3d</li> <li>Incubation period HUS +7d</li> <li>bloody diarrhea:60%</li> <li>HUS in 15%</li> <li>Neurological symptoms: 25%</li> </ul>	<ul style="list-style-type: none"> <li>n&gt; 810</li> <li>Adults: 49 (22-87); Children (11, 4-15)</li> <li>EHEC O104:H4/ESBL</li> <li>Incubation period diarrhea 8d</li> <li>Incubation period HUS +5d</li> <li>bloody diarrhea:83%</li> <li>HUS in 20%-25%</li> <li>Neurological symptoms: 35%</li> </ul>



A Webber Training Teleclass  
[www.webbertraining.com](http://www.webbertraining.com)



# The New Gram-Negative Challenge

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## Is it a new strain...?

**O104:H4**

HUSEC41, firstly identified in Germany 2001 in two siblings

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

EAEC

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

EHEC

typical EHEC loci  
(stx2, iha, IpfO26, IpfO113)

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

Reservoir ?  
??

?

Primary source  
„fennugreek“ et al.

outbreak source

2nd source

## EHEC on fruits and veg

Year	Strain	Environment	Survival (day)	References
1997	<i>E. coli</i> O157:H7	Sprouted seeds (alfalfa)		Swaglasingham et al. 2004
1997	<i>E. coli</i> O157:H7	Salad		Anon (2005a)
1998	<i>E. coli</i> O157:H7	Salad		Anon (2001a,b)
1998	<i>E. coli</i> O157:H7	Fruit salad		Anon (2001a,b)
1998	<i>E. coli</i> O157:H7	Coleslaw		Anon (2001a,b)
1998	<i>E. coli</i> O157:H7	Sprouted seeds (clover/alfalfa)		Taormina et al. 1999
1998	<i>E. coli</i> O157:H7	Unpasteurized apple juice		Anon (2001a,b)
1998	<i>E. coli</i> O157:H7	Parsley		Swaglasingham et al. 2004
1999	<i>E. coli</i> O157:H7	Cress (iculant)		Campbell et al. 2001
1999	<i>E. coli</i> O157:H7	Unpasteurized apple juice		Anon (2001a,b)
2003	<i>E. coli</i> O157:H7	Cucumber		Duffell et al. (2003)
2003	<i>E. coli</i> O157:H7	Lettuce		Anon (2005a)
2005	<i>E. coli</i> O157:H7	Lettuce		Söderström et al. (2005)
2006	<i>E. coli</i> O157:H7	Spinach		CDC (2006b)
2006	<i>E. coli</i> O157:H7	Lettuce		CDC (2006c)

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

Heaton and Jones, J Appl Microbiol 2007

## Stx-genes: common in nature

PubMed search results for "Stx-genes: common in nature" and "Phage-mediated Shiga toxin 2 gene transfer in food and water."


## This time Innocent

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## 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



**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 carries 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

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**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 – Diarrhea 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?

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




Thank you!