The Case for Antimicrobial Copper

breaking the chain of infection

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UNIVERSITY OF Southampton

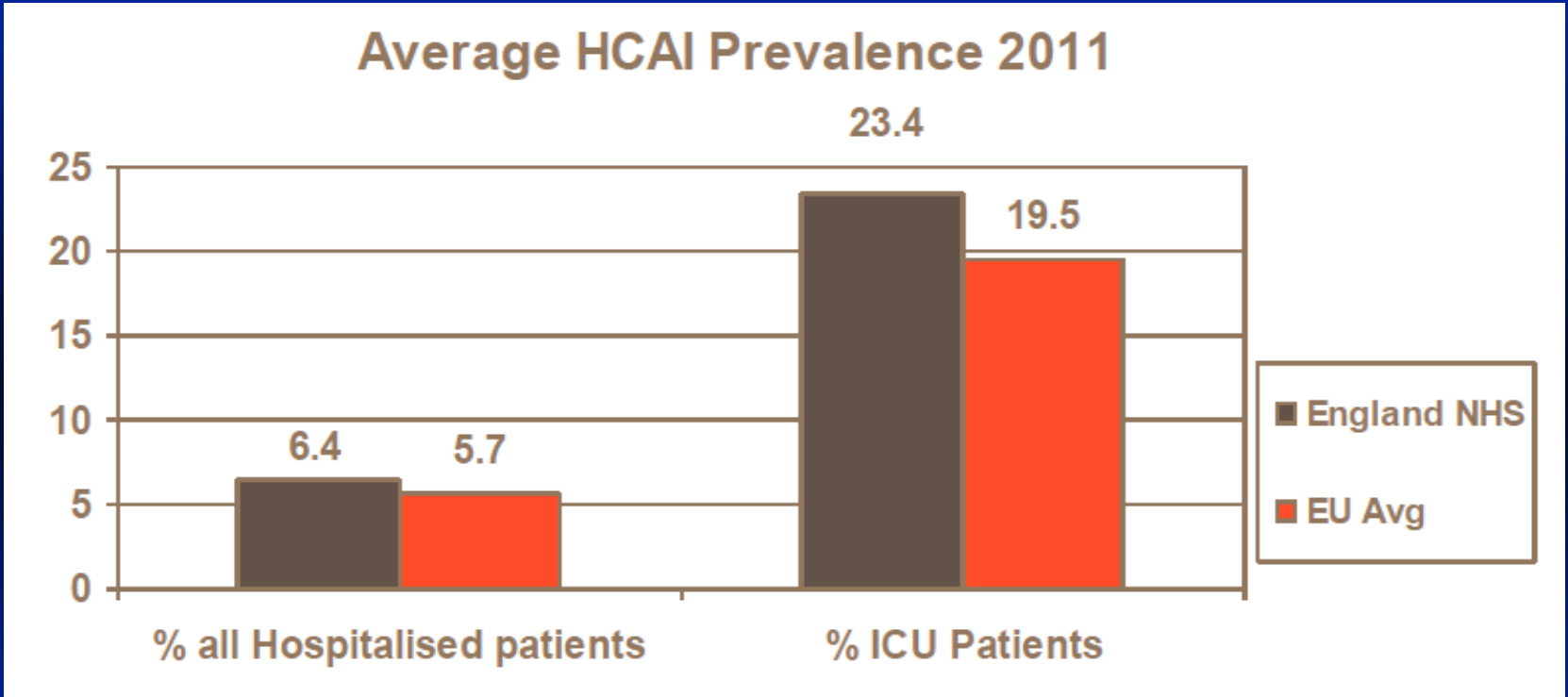
Environmental Healthcare Unit

If one full wide bodied jet was lost each day would anyone fly?

350 US patients die *every day* from HCAIs

M. Schmidt

Healthcare-Associated Infections in EU



Up to 51% prevalence in ICUs within EU countries

Source: WHO - The Burden of HealthCare-Associated Infection Worldwide – A Summary. 2011
WHO - European Health for All Database (HFA-DB)

HCAIs in Europe – the grim facts

Each year:

- Over **4.1 million** patients affected
- **16 million** extra days in hospital
- Additional **€7 billion** direct costs
- **37,000** deaths directly caused by HCAIs
- Additional **110,000 deaths** where HCAIs a contributory factor
- **80% of infections** spread by touch
- Clinical trials have identified **shortcomings** in use of hand decontamination measures e.g. alcohol rubs, soap & water

Source: WHO - The Burden of HealthCare-Associated Infection Worldwide – A Summary. 2011
WHO - European Health for All Database (HFA-DB)

CONTAMINATION OF CONTACT SURFACES IN BUILDINGS AND MASS TRANSPORT

How many times a day are contact surfaces cleaned?

How frequently do people wash hands?

Dissemination of respiratory and faecal pathogens

Rise of the “Superbugs”

- 70% of HCAI are antibiotic resistant, many broad spectrum

- MRSA
- VRE
- *Clostridium difficile* spores

- ESBL e.g. *Acinetobacter baumannii, E. coli, P. aeruginosa*
- *Klebsiella pneumoniae* carbapenemase Class A (*KPC*) 1996
- New Delhi Metallo-1 beta lactamase Class B *(NDM-1)* 2009

- Numerous studies show:
- survive for days/weeks on various surface materials;
- ESBL outbreaks suggest environmental transmission may be important

‘KPC’ Mar 07, 2014 By Andrew Gregory

Superbug kills 17 people and hundreds have been infected by bacteria highly resistant to antibiotics

Sixteen people have died in the Central Manchester University Hospitals NHS trust area in the past four years – and another died at Wolverhampton's New Cross

Danger: The Klebsiella pneumoniae bacterium

The Global Concern

The Times May 2016

Antibiotic resistance is now as serious a *threat* as *terrorism* and could trigger an 'apocalyptic scenario', warns UK's *top* doctor.

24th January 2013

“Bacteria could become resistant to antibiotics, taking the UK 'back to the dark ages”

Express 2nd July, 2014

"Unless we take global action, antimicrobial resistance will become an even greater threat to mankind than cancer ..”

Kill as many as 10 million people by 2050, one every 3 seconds
Cost $100 trillion

Telegraph April 14, 2016

Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

FINAL REPORT AND RECOMMENDATIONS

May 2016

CHAIRED BY JIM O'NEILL

One person will die every 3 seconds from drug resistant bacteria

UN meeting tackles the 'fundamental threat' of antibiotic-resistant superbugs

All 193 UN member states sign declaration agreeing to combat the proliferation of drug-resistant infections, estimated to kill more than 700,000 people each year.

In two years, groups including UN agencies will provide an update on the superbug fight to the UN secretary general

20th September 2016

CAUSES OF ANTIBIOTIC RESISTANCE

HANDLE ANTIBIOTICS WITH CARE

Antibiotic resistance happens when bacteria change and become resistant to the antibiotics used to treat the infections they cause.

Over-prescribing of antibiotics

Patients not finishing their treatment

Over-use of antibiotics in livestock and fish farming

Poor infection control in hospitals and clinics

Lack of hygiene and poor sanitation

Lack of new antibiotics being developed

www.who.int/drugresistance

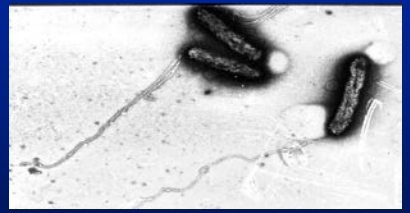
#AntibioticResistance

World Health Organization

ANTIMICROBIAL COPPER

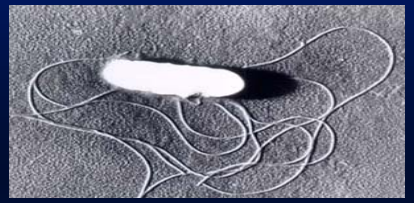
Water-borne pathogens in biofilms

- *Legionella pneumophila*, *Helicobacter pylori*
- *E. coli* O157



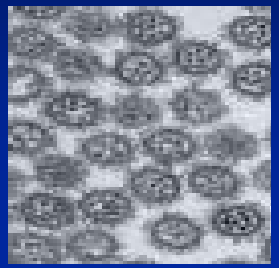
Food-borne pathogens on surfaces

- *E. coli* O157, *Salmonella*
- *Listeria monocytogenes*



Hospital-acquired pathogens

- MRSA, VRE, *C. difficile*,
- *A. baumannii*, CRE, *K. pneumoniae* NDM-1 *etc*

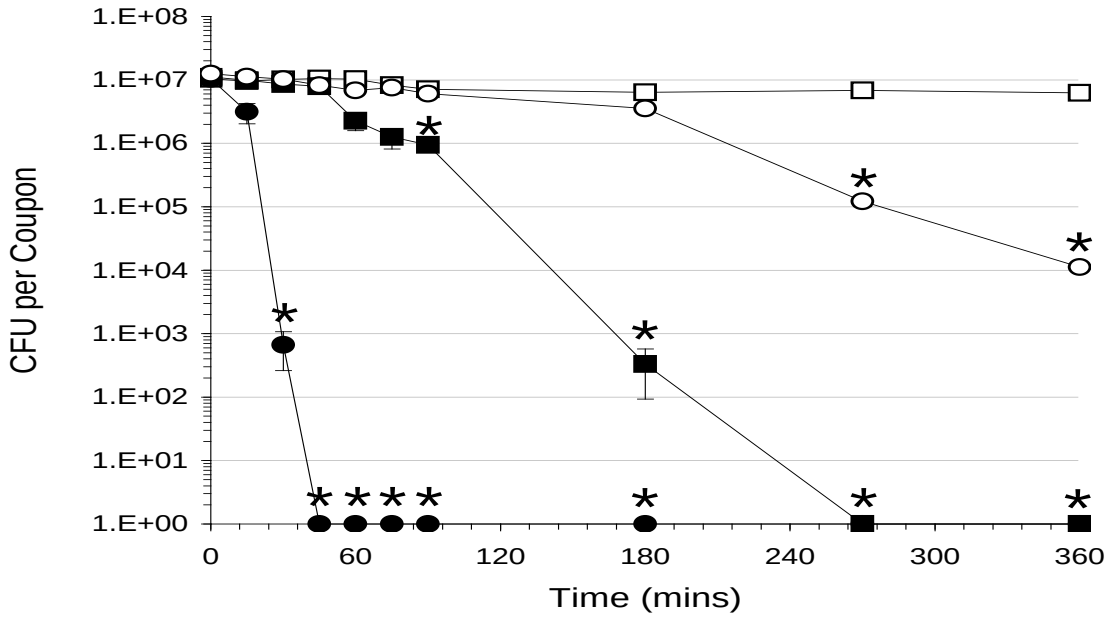


- Viruses - influenza H1N1, norovirus, adenovirus, coronavirus
- Fungi- *Candida*, *Aspergillus* (HVAC systems)

Moist contact model

MRSA on Stainless Steel (□), C19700 (●), C24000 (■) and C77000 (⬭) at 20°C

Moist test simulating coughs, sneezes etc (20 µL inoculum)



or Silver for 24h

* Indicates p=<0.05 compared to zero time controls

Noyce *et al*., JHI 63, 289-297 (2006)

ENVIRONMENTAL SURVIVAL OF KEY PATHOGENS ON HOSPITAL SURFACES

Pathogen	Survival Time
S. aureus (including MRSA)	7 days to >12 months
Enterococcus spp. (including VRE)	5 days to >46 months
Acinetobacter spp.	3 days to 11 months
Clostridium difficile (spores)	>5 months
Norovirus (and feline calicivirus)	8 hours to >2 weeks
Pseudomonas aeruginosa	6 hours to 16 months
Klebsiella spp.	2 hours to >30 months

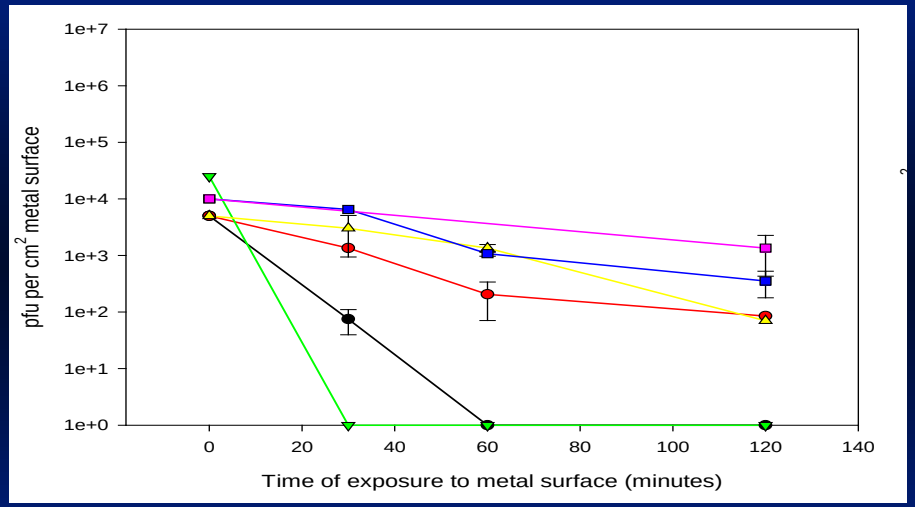
Adapted from Hota B, et al. Clin Infect Dis 2004;39:1182-9 and
Kramer A, et al. BMC Infectious Diseases 2006;6:130

Dry touch surface model

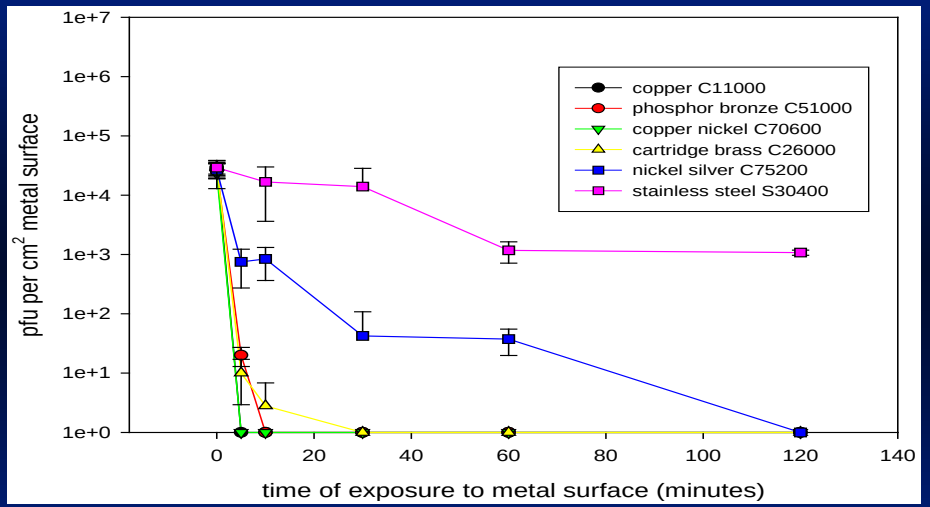
Norovirus inactivation on copper surfaces

>267m infections p.a.

MOIST



DRY

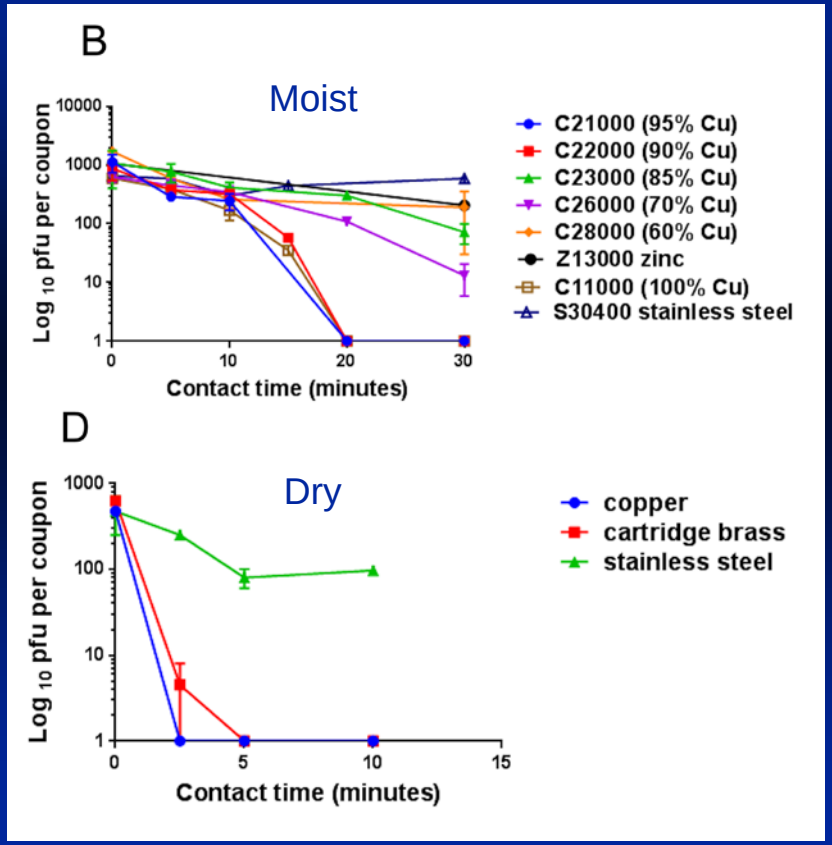


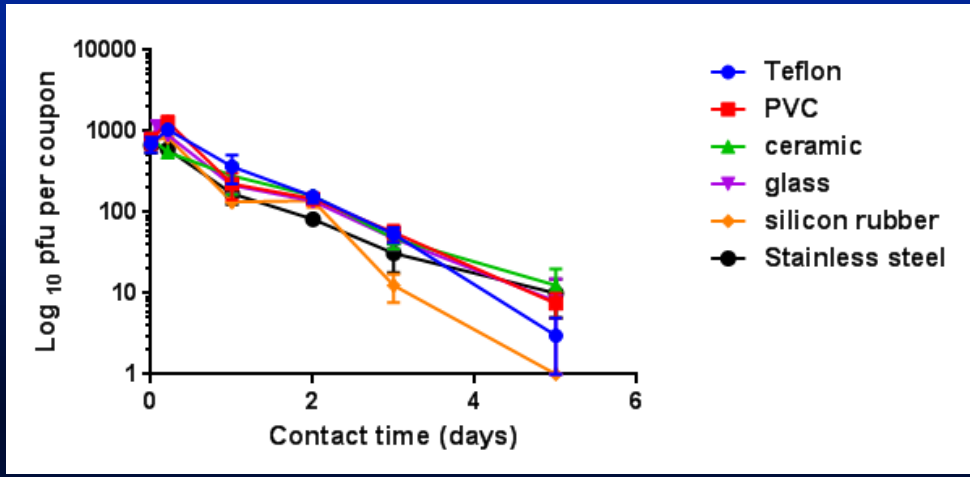
- for 'wet' inoculum rapid loss of viral infectivity occurs on copper and copper nickel with significant reduction after 2 hours contact
- plus phosphor bronze for dry inoculum, with complete inactivation in several minutes
- nickel silver takes a little longer

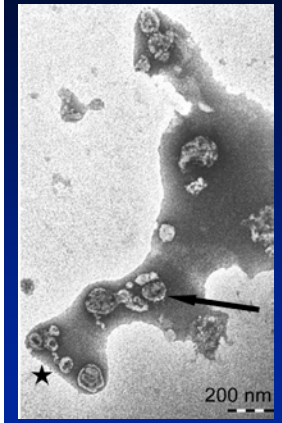
Warnes and Keevil, PLoS ONE 8, e75017 (2013)

HuCoV-229E surface inactivation

Non-copper surfaces

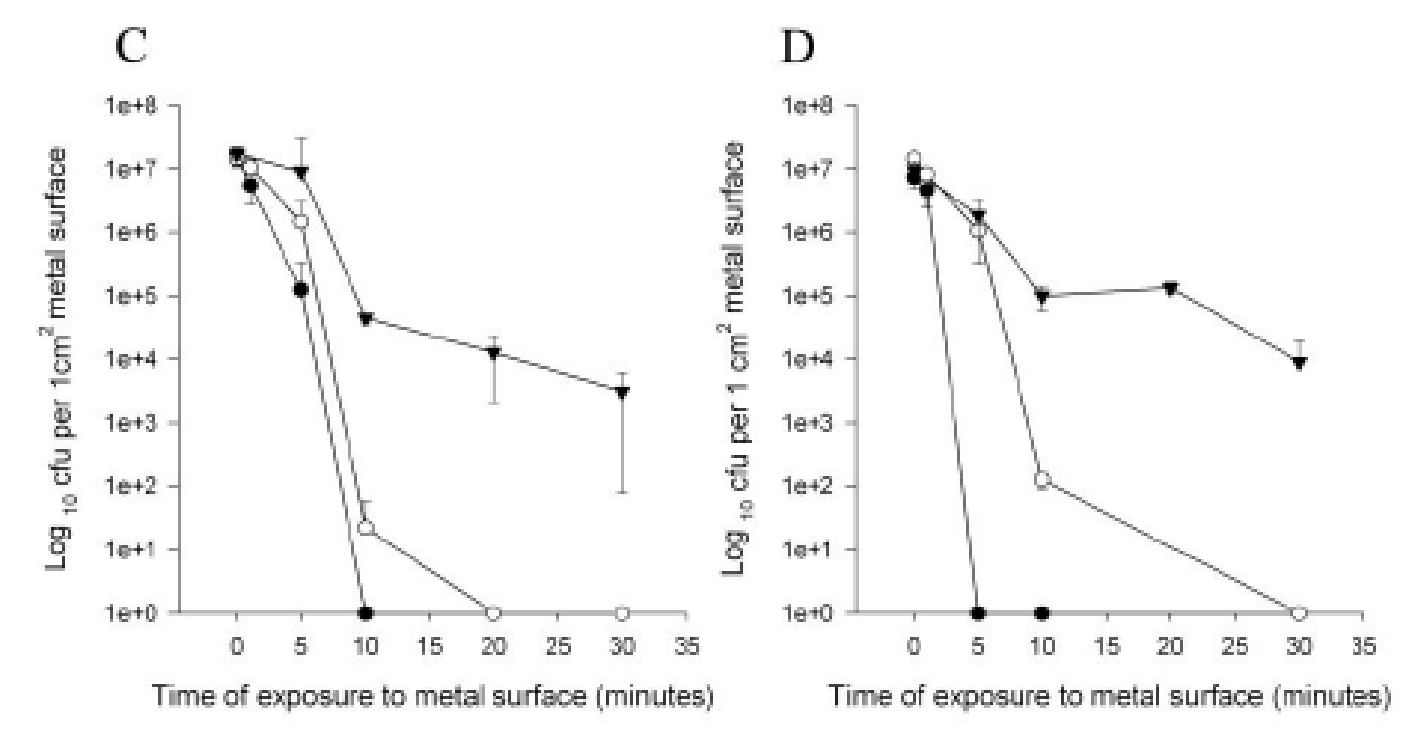






Warnes *et al.*, mBio 6, e01697-15 (2015)

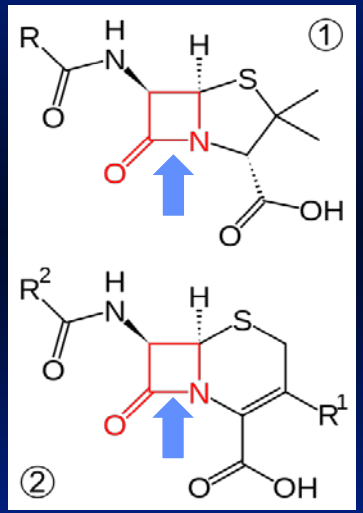
Rapid inactivation of dry challenge *E. coli* and *S. typhimurium* on copper, brass and stainless steel

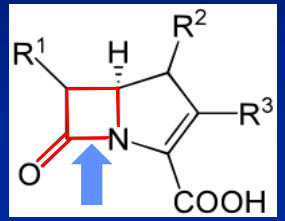


Warnes *et al*., Environ. Microbiol. 14, 1730–1743 (2012)

Evolution of β-lactamase to carbapenamases e.g. *bla*$_{NDM-1}$

December 2009, after unsuccessful treatments in hospitals in New Delhi, a Swedish national was referred back to a Swedish hospital, where it was discovered that he had acquired an antibiotic-resistant bacterial infection during his stay in India; infected with ***Klebsiella pneumoniae*** (Gram-negative bacterium found in the normal flora of the mouth, skin, and intestines) infection.
NDM-1 gene now found in **India, Pakistan, Bangladesh, Australia, Canada, the Netherlands, United States, UK.**
Carbapenamases hydrolyse carbapenems called **'antibiotics of last resort'.**



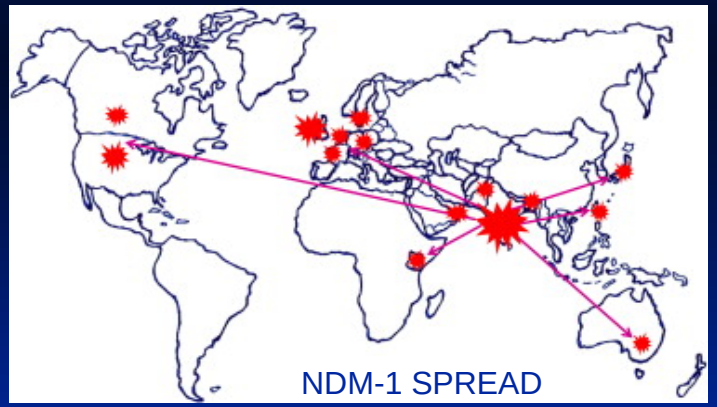


1. Penicillins
   - β-lactamases

2. Cephalosporins
   - BS β-lactamases

3. Cephalosporins e.g. cefoxatime
   - ESBL:
- CTX, OXA, TEM

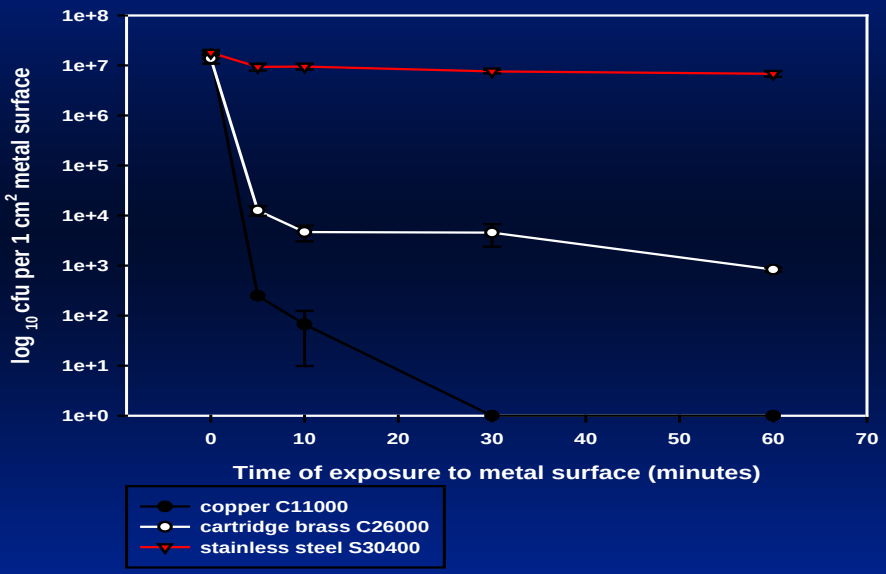
3. Carbapenems e.g. meropenem
   - KPC, NDM-1



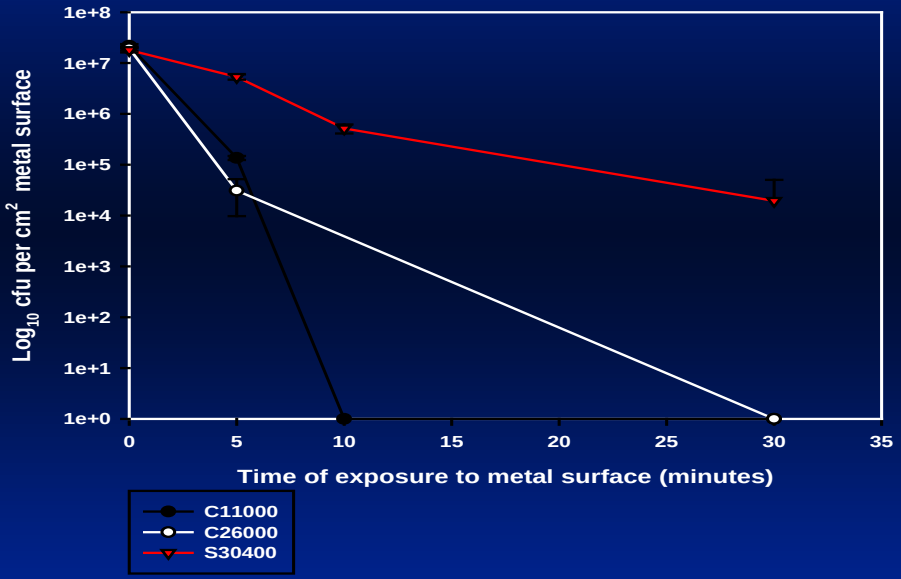
'antibiotics of last resort'

Survival of ESBL producing *E. coli bla CTX-M-15* on metal surfaces: 'dry' inoculum

Cells in bacteriological medium (BHIB)



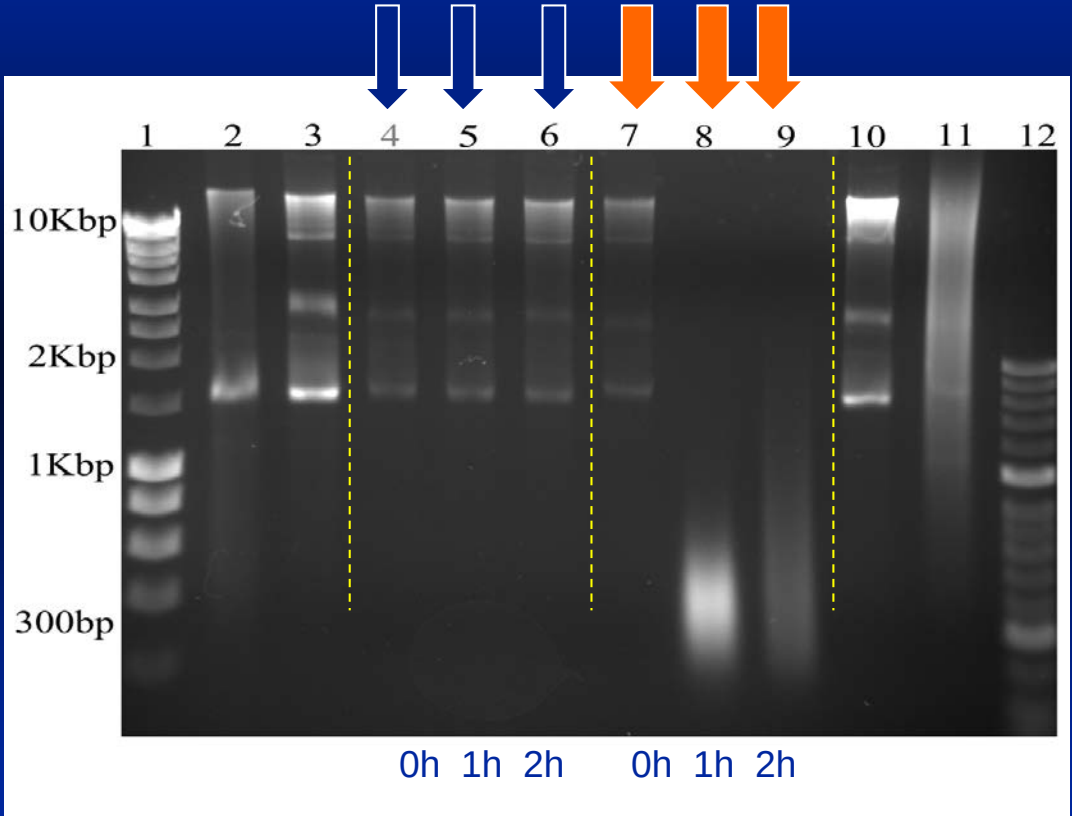
Cells in PBS



Cells in PBS die very quickly on copper and copper alloy surfaces.
As for 'wet' inoculum the death-rate is reduced if cells are inoculated in complex matrix particularly at lower copper concentrations

Warnes *et al*. mBio 3, e00489-12 (2012)

Destruction of plasmid DNA of *E. coli bla CTX-M-15* following exposure to copper at room temperature



Cells exposed to stainless steel for 0, 60 and 120 minutes (lanes 4, 5,6 respectively) have intact plasmid DNA

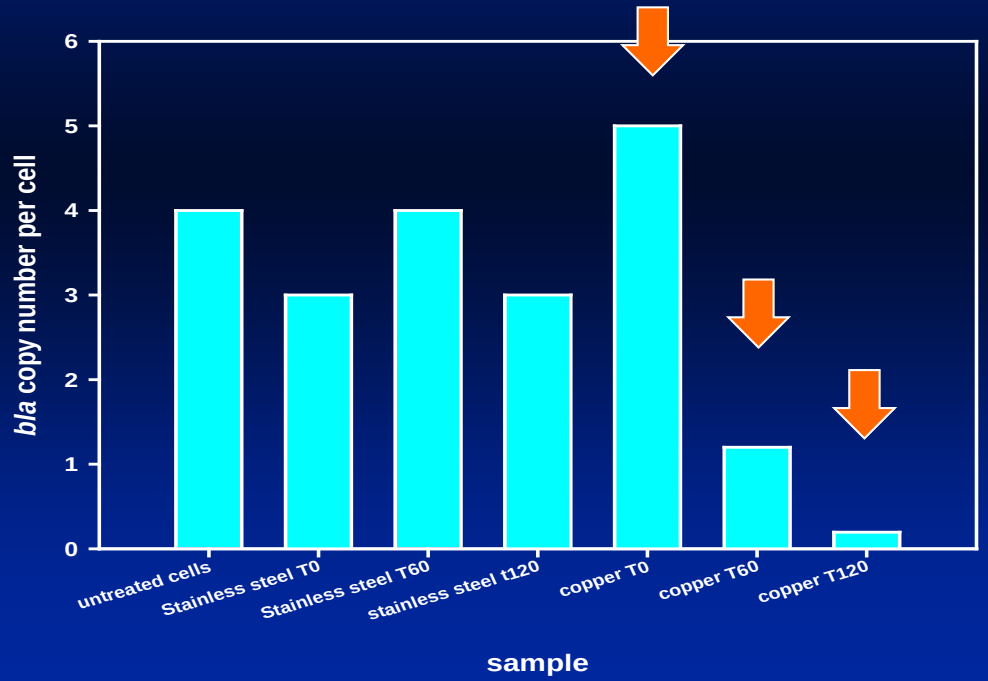
Cells exposed to copper surfaces for 0, 60 and 120 minutes (lanes 7, 8, 9) demonstrate progressive denaturation of plasmid DNA over time.

Lanes 10, 3 untreated cells
Lane 11 is heated cells

Warnes *et al*. mBio 3, e00489-12 (2012)

Direct detection of the *CTX-M-15 bla* gene in the same plasmid preparations using quantitative PCR (qPCR)

Copy number of beta lactamase gene in antibiotic resistant *E. coli* (untreated cells or those exposed to copper and stainless steel surfaces at room temperature: 'wet' inoculum)

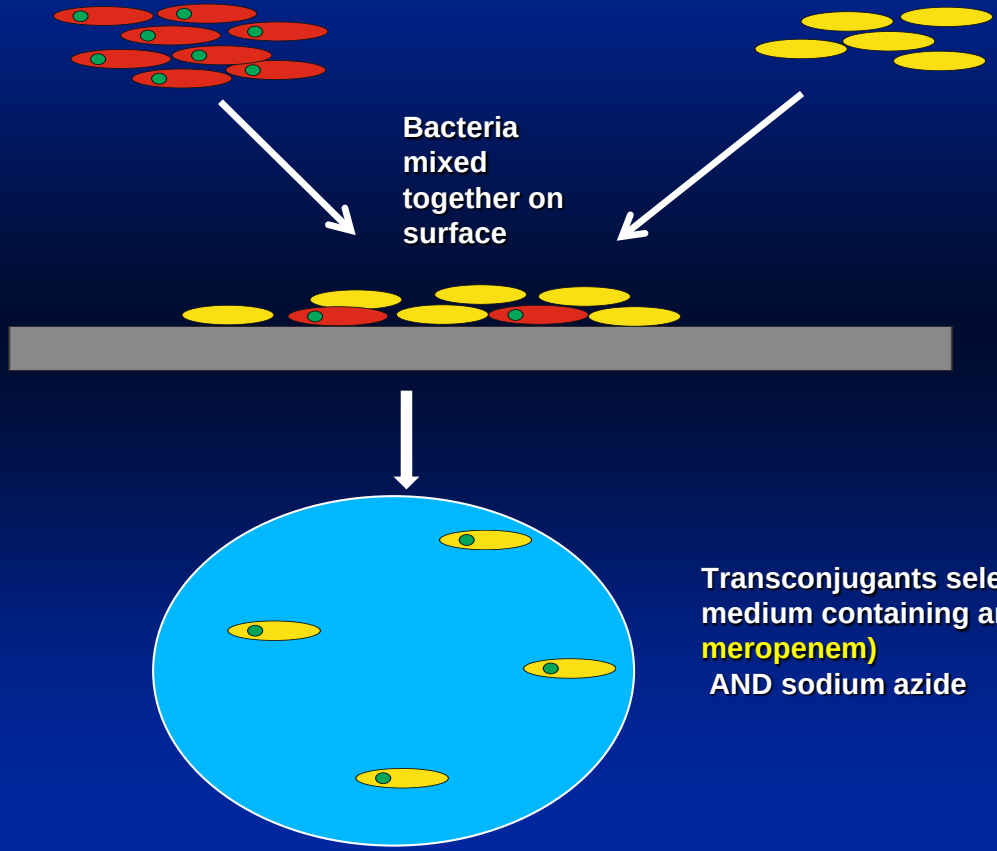


If the cT values are converted to actual gene copy number per cell it can be seen that copy number has depleted over time when exposed to copper surfaces.

Warnes *et al*. mBio 3, e00489-12 (2012)

Can antibiotic resistance genes be transferred by natural conjugation on surfaces?

Pathogen containing antibiotic resistance gene on plasmid (green) e.g. *K. pneumoniae* NDM-1 and *E. coli* CTX-M-15 DONOR, sensitive to sodium azide



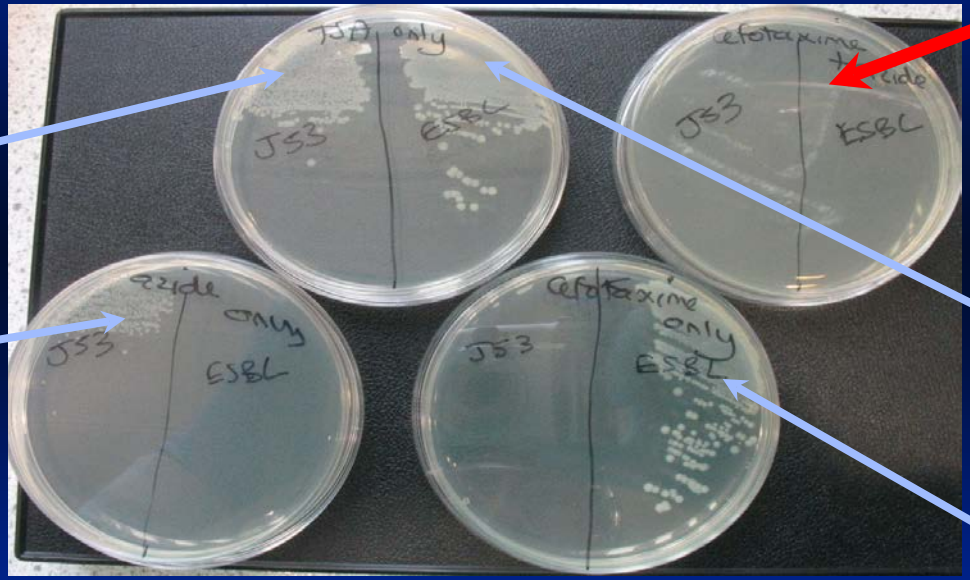
Bacteria mixed together on surface

***E. coli* RECIPIENT strain, resistant to sodium azide but sensitive to antibiotic**

Transconjugants selected for growth on medium containing antibiotic (e.g. cefotaxime, meropenem) AND sodium azide

Bacterial cultures checked prior to conjugation experiment

Recipient strain *E. coli* J53 grows on non-selective tryptone soy agar (TSA) and medium containing **sodium azide**



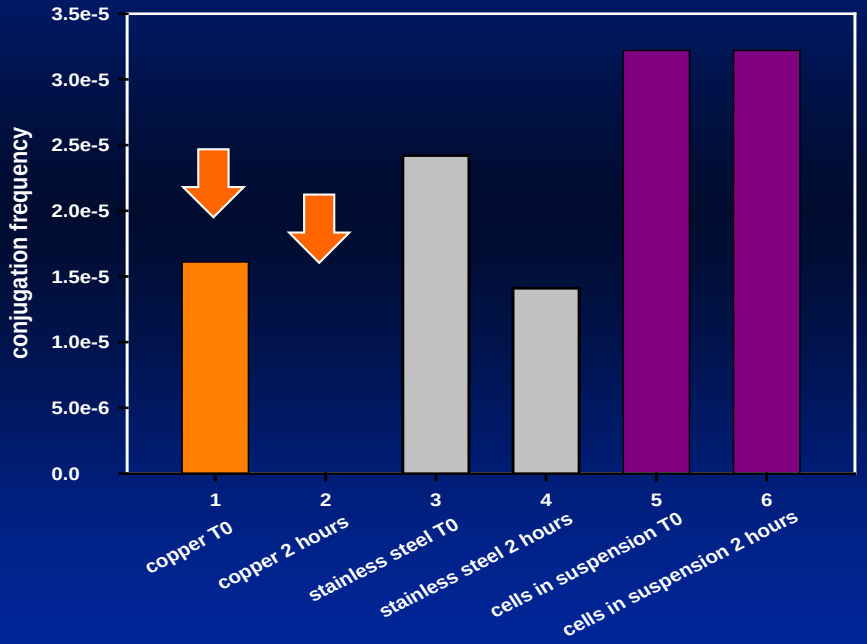
Neither strain grows on medium containing antibiotic AND sodium azide

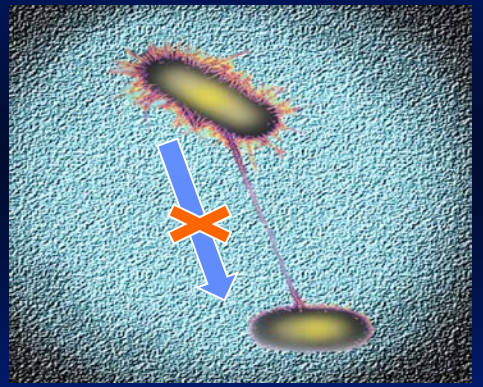
Donor strain grows on TSA and medium containing antibiotic, **cefotaxime**

Detection of *bla CTX-M-15* in possible transconjugants

(selected by ability to grow on medium containing cephalosporin and sodium azide)

Frequency of transfer of beta lactamase gene to recipient strains on metal surfaces





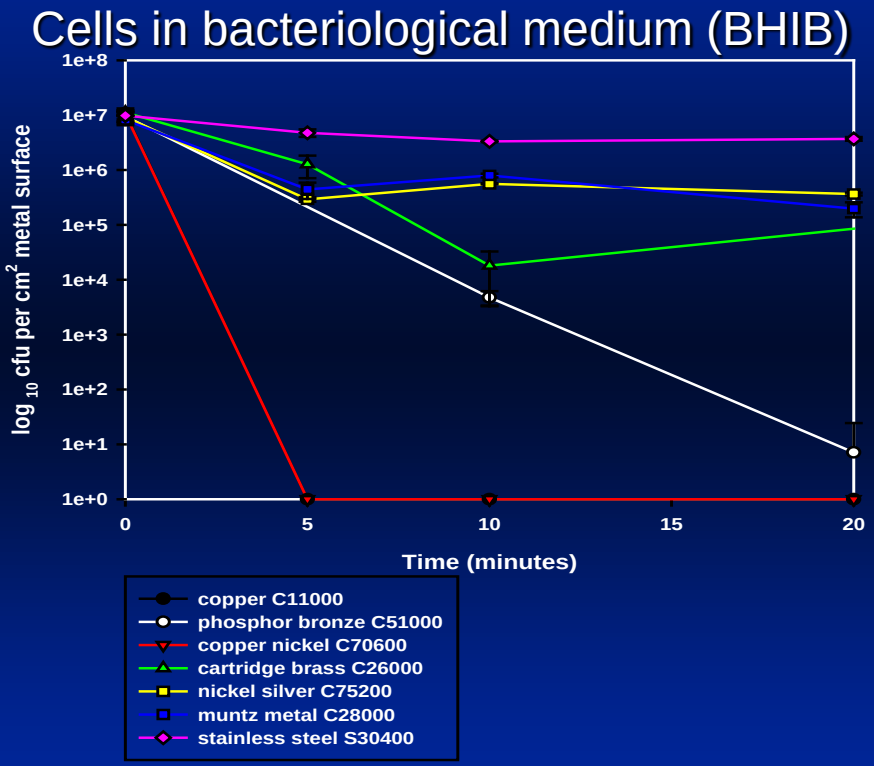
www.flickr.com

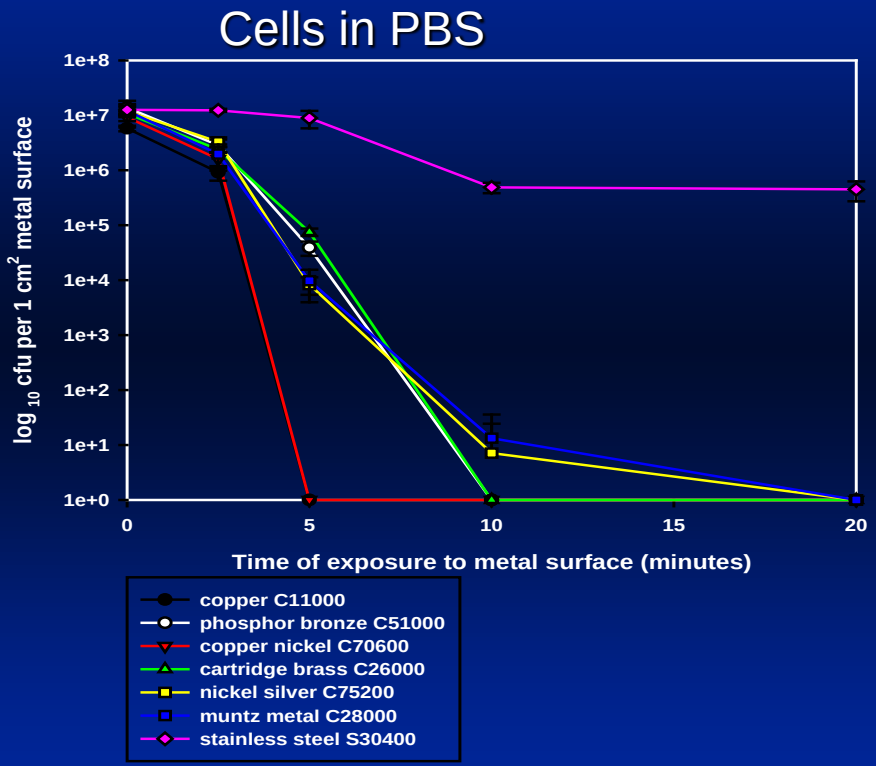
Cu prevents transfer

Conjugation frequency = no. transconjugants /no. donor cells

Warnes *et al*. mBio 3, e00489-12 (2012)

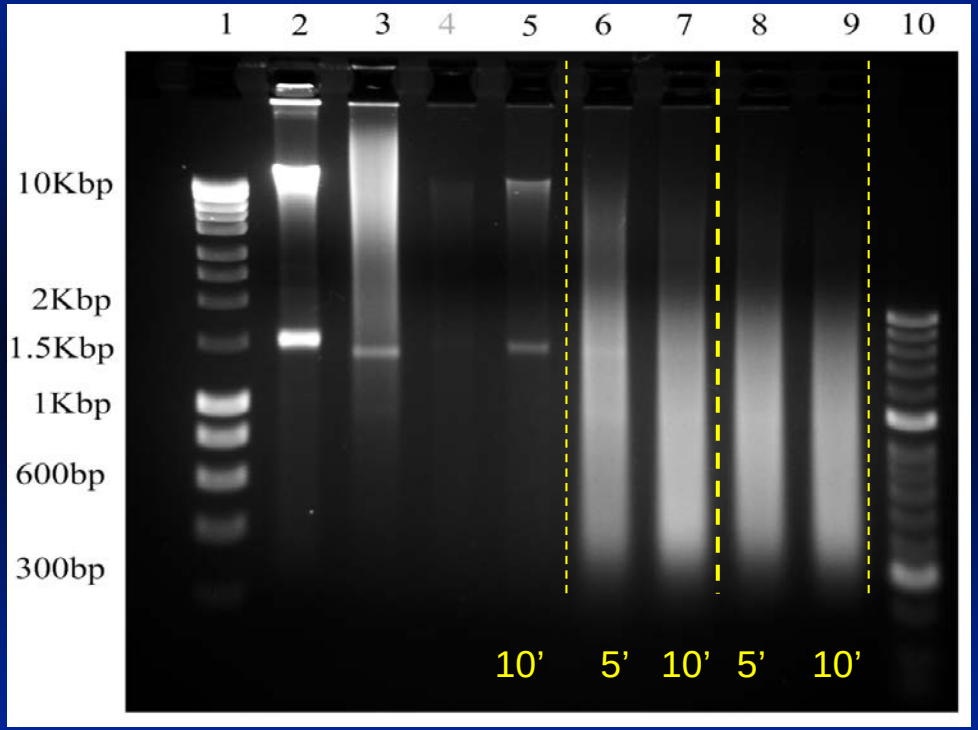
Survival of *bla* NDM-1 producing *K. pneumoniae* on metal surfaces: 'dry' inoculum





Warnes *et al*. mBio 3, e00489-12 (2012)

Exposure to copper or cartridge brass degrades plasmid DNA of MDR-*Klebsiella pneumoniae* (‘dry’ touch contamination)



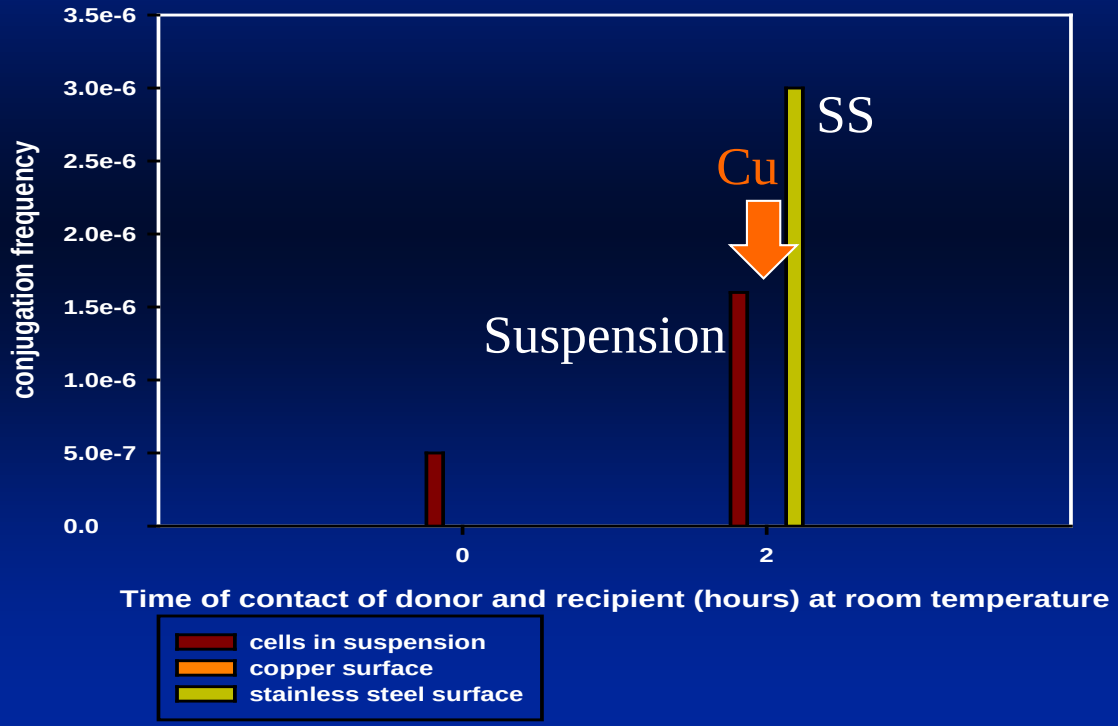
Degradation of *K. pneumoniae* plasmid DNA occurs on copper (lanes 8, 9: 5 and 10 minutes contact respectively) and cartridge brass (lanes 6, 7 :5 and 10 minutes contact) but not on stainless steel (lane 5: 10 minutes).

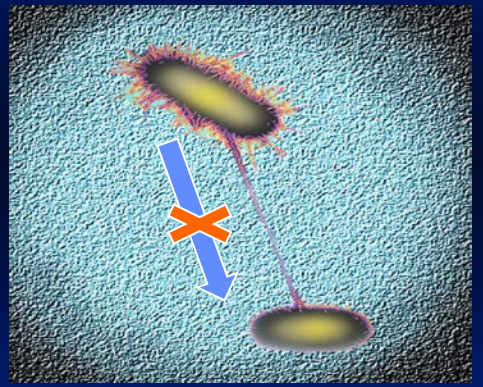
Degraded DNA appears as a ‘smear’ of multi-sized fragments. This can be seen clearly in the small 1.5Kbp plasmid which is evident on untreated, heat-killed and cells exposed to stainless steel for 10 minutes but not on copper or alloy (although faint band can be seen after 5 minutes contact on alloy)

Warnes *et al*. mBio 3, e00489-12 (2012)

Horizontal transfer of *K. pneumoniae bla* $_{NDM-1}$ occurs in suspension and on stainless steel surfaces

Frequency of transfer of *bla* $_{NDM-1}$ to recipient cells on surfaces or in suspension.





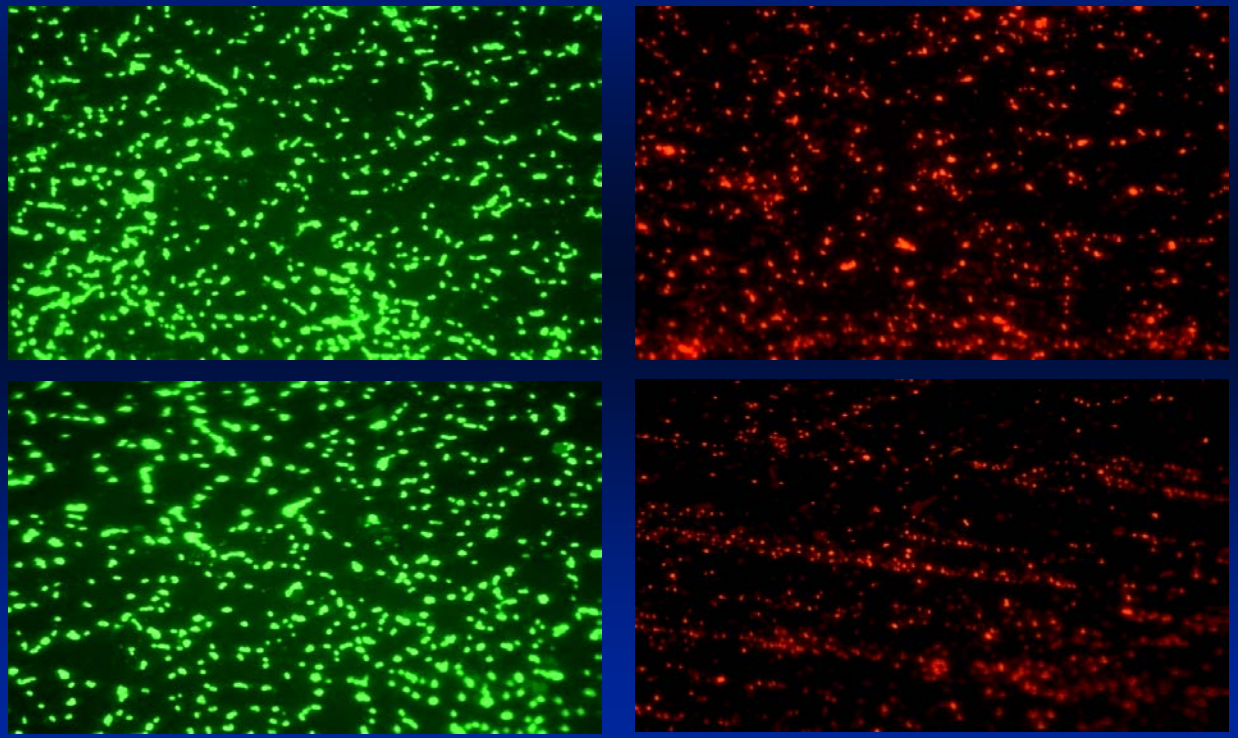
www.flickr.com

Cu prevents transfer

Warnes *et al*. mBio 3, e00489-12 (2012)

Gram-positive **VRE DNA content and respiration on stainless steel (inoculum 10^6 cfu per cm^2; 4h)**

Dry test simulating hand contact (1 μL inoculum)



E. faecalis

E. faecium

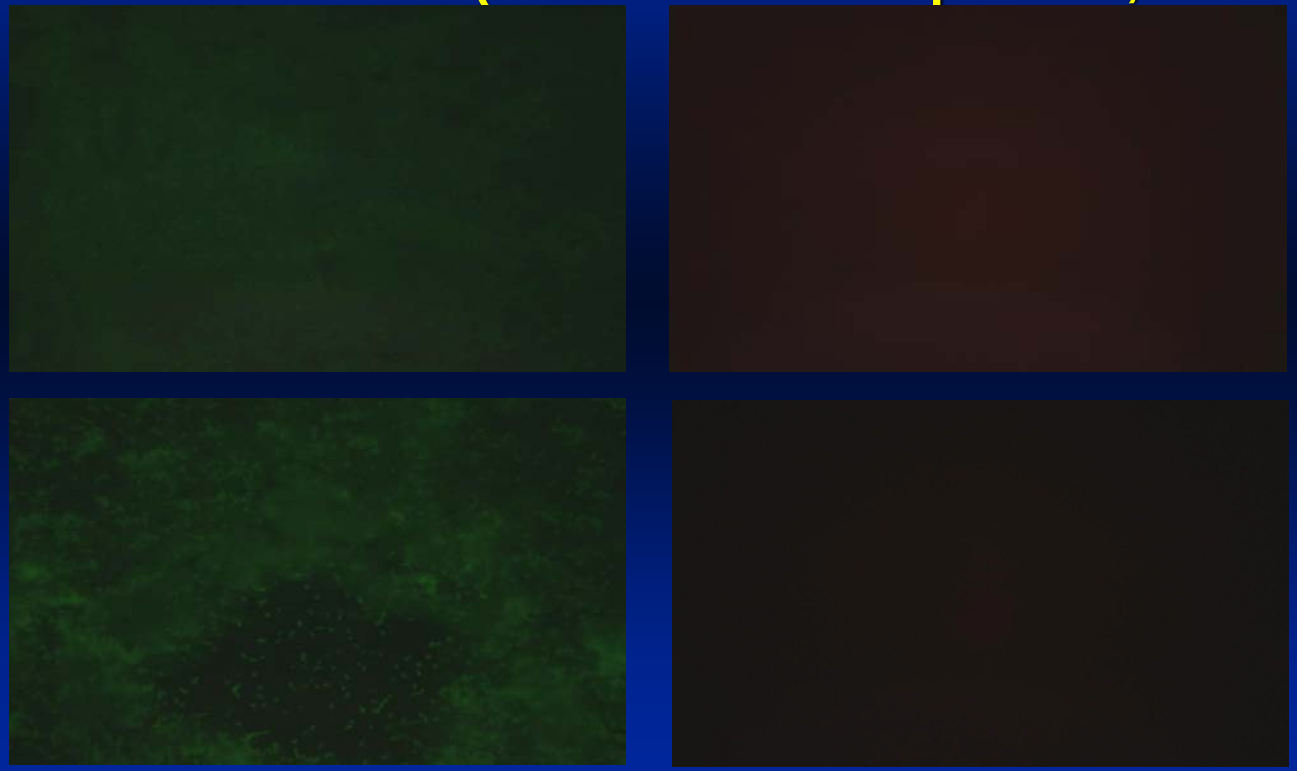
SYTO9

CTC

Warnes and Keevil, AEM 77, 6049-59 (2011)

Destruction of VRE DNA and respiration on copper

(inoculum 10^6 cfu per cm^2; 10 min)



E. faecalis

E. faecium

SYTO9

CTC

Warnes and Keevil, AEM 77, 6049-59 (2011)

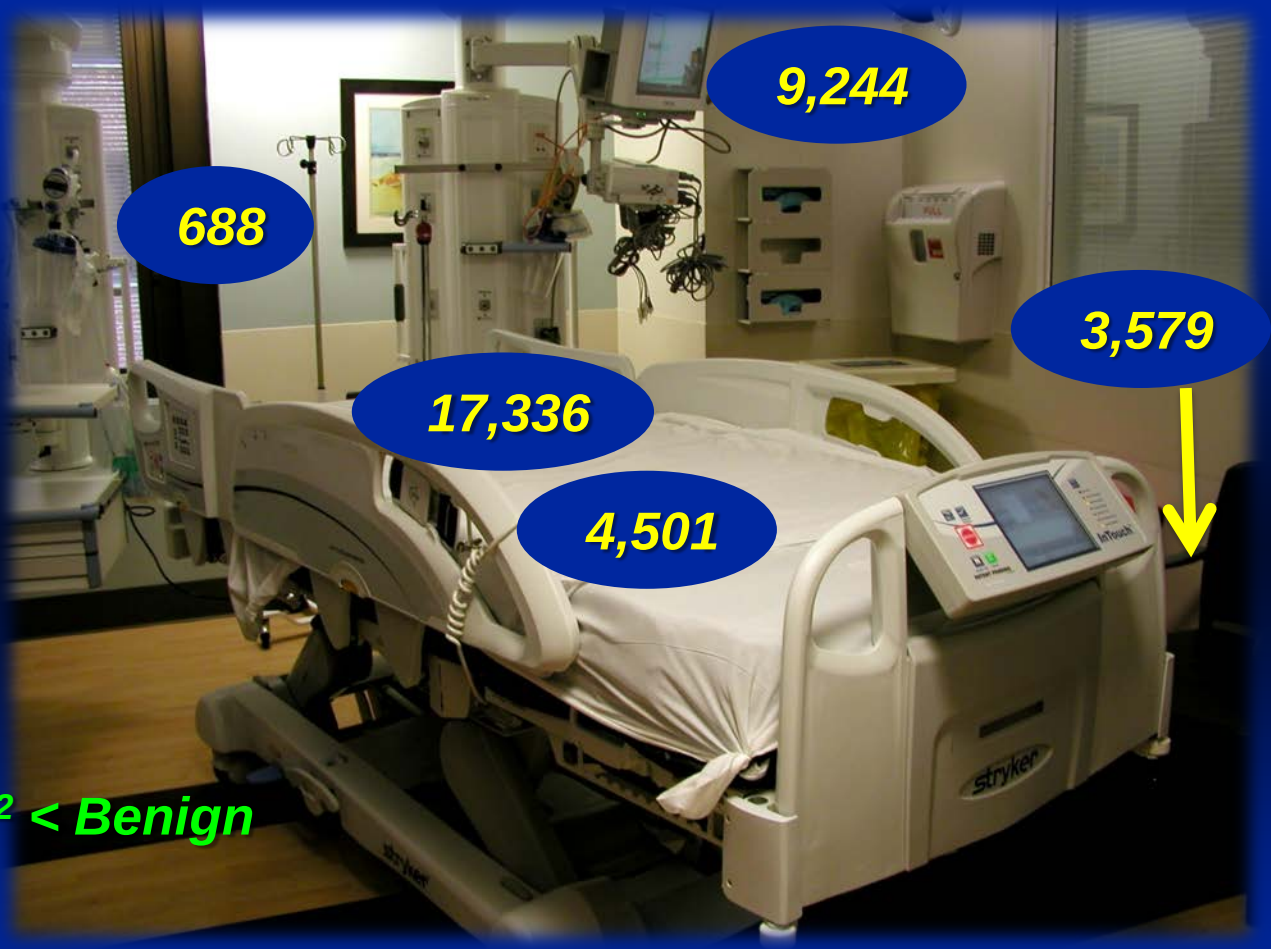
Conclusions

- Contact surfaces are hitherto unrecognised reservoir for rapid HGT and emergence of superbugs
- Copper alloys kill rapidly, particularly on dry contact
- Continuous activity 24/7 through Cu(I)/(II) and ROS

- Rapid destruction of genomic and plasmid nucleic acid could:
  - prevent mutational resistance developing
  - help reduce the spread of antibiotic resistance genes to receptive and potentially more virulent organisms
  - as well as genes responsible for virulence and toxin production.

- Combination of effective cleaning regimes and contact surfaces containing copper could be invaluable to prevent spread of viable pathogens and AMR.

INTERVENTION WITH COPPER



250/100cm² < Benign

When we look, the risk is omnipresent!

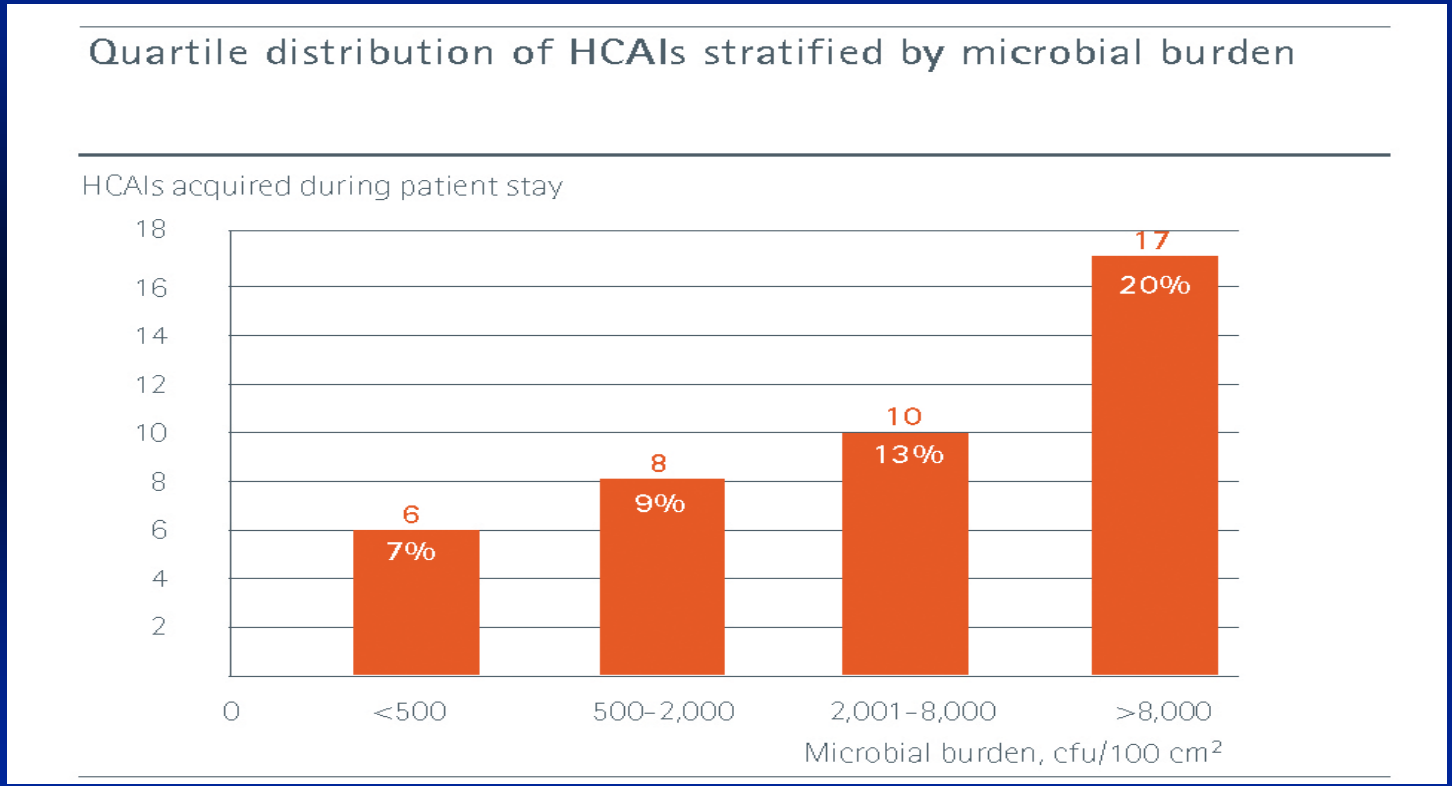
M. Schmidt

Risk was Significantly Lower with Copper

16 rooms sampled weekly for a period of 21 months, n=1012

Schmidt *et al*., JCM 50, 2217-2223 (2012)

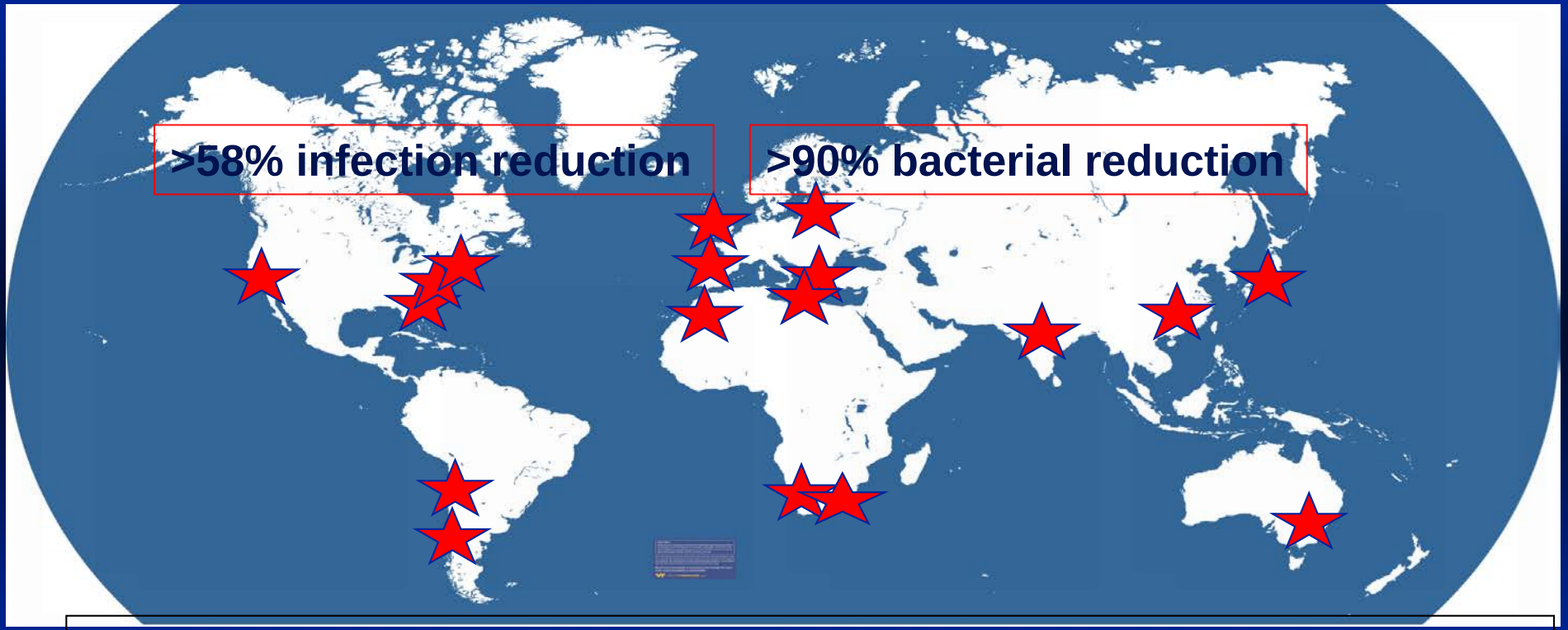
Link between environmental bioburden and acquisition of HCAIs reported



89% of HCAIs occurred among patients in rooms with a bioburden > 500 cfu/100cm^2

Salgado *et al*., ICHE 34, 479-486 (2013)

Ward Trials Worldwide



HCAIs: 8.43% **58.1% reduction** HCAIs: 3.4%

(p= 0.013)

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevierhealth.com/journals/jhin

epic3: National Evidence-Based Guidelines for Preventing Healthcare-Associated Infections in NHS Hospitals in England

H.P. Loveday[a*], J.A. Wilson[a], R.J. Pratt[a], M. Golsorkhi[a], A. Tingle[a], A. Bak[a], J. Browne[a], J. Prieto[b], M. Wilcox[c]

Recognised that high-touch surfaces made of antimicrobial copper alloys harbour 80–90% fewer bacteria than equivalent, non-copper surfaces in busy wards undergoing routine cleaning worldwide.

Summary

- Superbugs are killed on copper alloy surfaces and antibiotic resistance gene transfer, which can easily occur, is abolished.
- Influenza, coronavirus and norovirus survive for extended periods on contemporary materials but are rapidly inactivated on copper alloy surfaces.
- epic3 guidelines recognise high-touch surfaces made of antimicrobial copper alloys harbour 80–90% fewer bacteria than equivalent, non-copper surfaces in busy wards undergoing routine cleaning worldwide.
- USA studies in 3 hospitals have demonstrated a 58% reduction in infection rate in ICUs

Copper alloy touch surfaces are an *additional* infection prevention measure

+

+

Works 24/7

Cu+™

Copper reduces bioburden and infection
Saves lives, saves £££

>400 Cu alloys now registered with US EPA with an antimicrobial claim – being deployed in healthcare, public buildings, public transportation etc

New build hospital, payback in 3 months

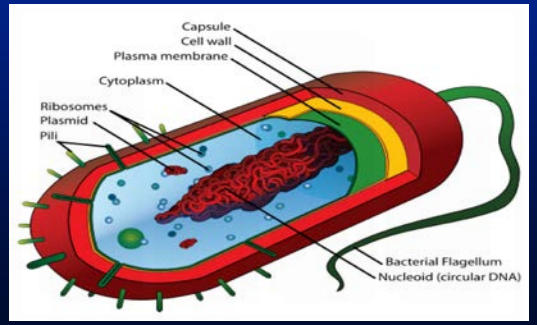
Acknowledgements

- University of Southampton:
  - Sarah Warnes, Callum Highmore
  - Sandra Wilks, Jonathan Noyce, Louise Weaver, Emma Goode

- Copper Alliance
  - Harold Michels

Cu Copper Alliance

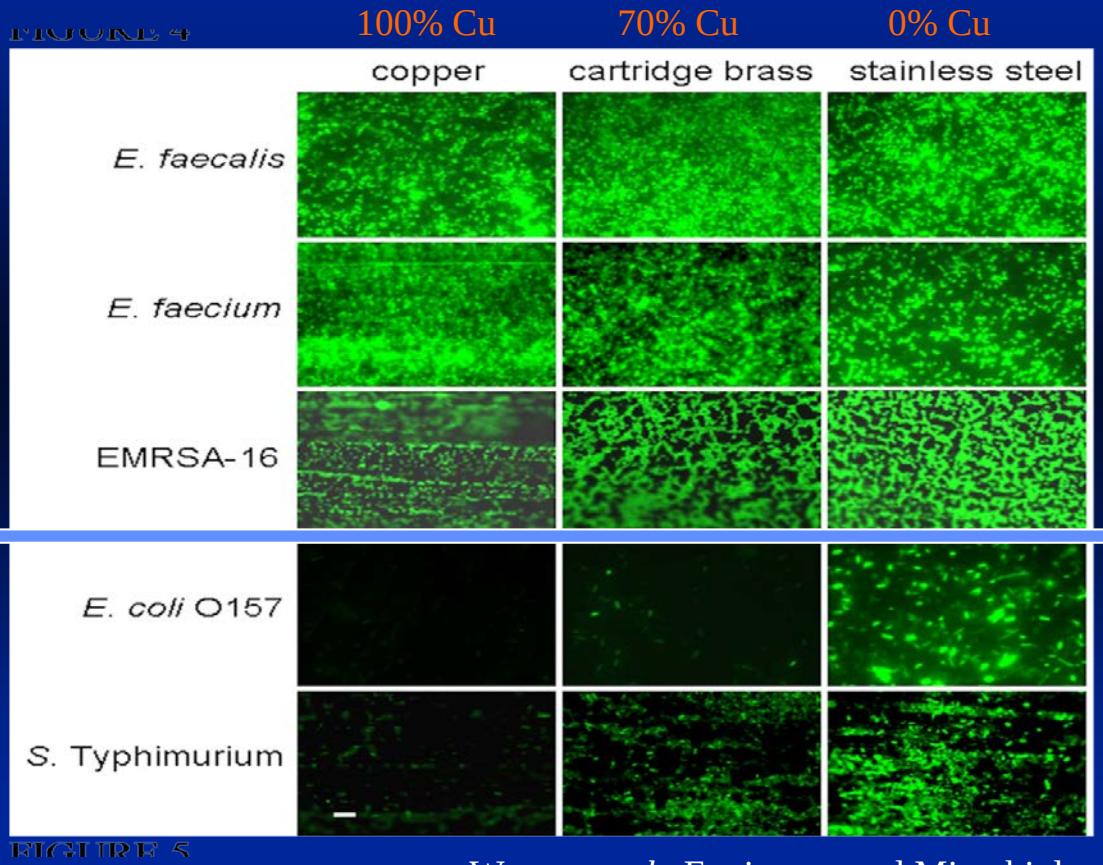
Bacterial metabolic suicide on Cu



$$Cu\ (I) + H_2O_2 \rightarrow Cu\ (II) + O_2 + OH^- + OH^{\cdot}$$

- Rapid 200,000x uptake of Cu(I) in seconds and attack
- Generation and attack by Reactive Oxygen Species

Copper disrupts membrane electrical potential in Gram negatives – 10 min exposure



Gram +ve

Gram -ve

Rhodamine 123 uptake

Warnes *et al*., Environmental Microbiology 14, 1730-43 (2012)