Antibióticos y Microbiosfera: Uso y abuso de AB

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Microbiosfera y equilibrio ecológico

Table 1. Microbes versus humans.

Variable	Microbes	Humans	Factor
No. on earth	5×10^{31}	6×10^{9}	$\sim 10^{22}$
Mass, metric tons	5×10^{16}	3×10^{8}	$\sim 10^{8}$
Generation time	30 min	30 years	$\sim 5 \times 10^{5}$
Time on earth, years	3.5×10^{9}	4×10^{6}	$\sim 10^{3}$

NOTE. Data are from [54].

La microbiosfera juega un papel fundamental en el equilibrio de los ecosistemas:

- Mineralización biomasa muerta
- Fijación de N
- Reciclaje de compuestos contaminantes
- Depuración del agua (humedales)
- síntesis de vit K, vit B12
- ...

200 especies patógenas para el hombre

Microbiosfera y ecosistema

- Desde hace miles de millones de años bacterias y hongos producen sustancias químicas que las protegen frente otros microorganismos (especies fluorescentes de *Pseudomona* producen fenazinas y lipopéptidos)

- En ambientes oligotróficos estos AB tienen una función de señalización y ordenamiento de comunidades microbianas.

- Algunas bacterias del suelo subsisten usando a los AB como única fuente de carbono

Microbiosfera y R natural a AB: Estrategia competitiva evolutiva

- Capacidad de mutación y selección:

  cepas con mecanismos de agresión, virulencia, capacidad de difusión y R.
- AB-R: fenómeno antiguo codificado por genes de resistencia que se transmiten de una generación de microorganismos a otra.
- Transferencia horizontal /lateral de ADN: intercambio genes de virulencia

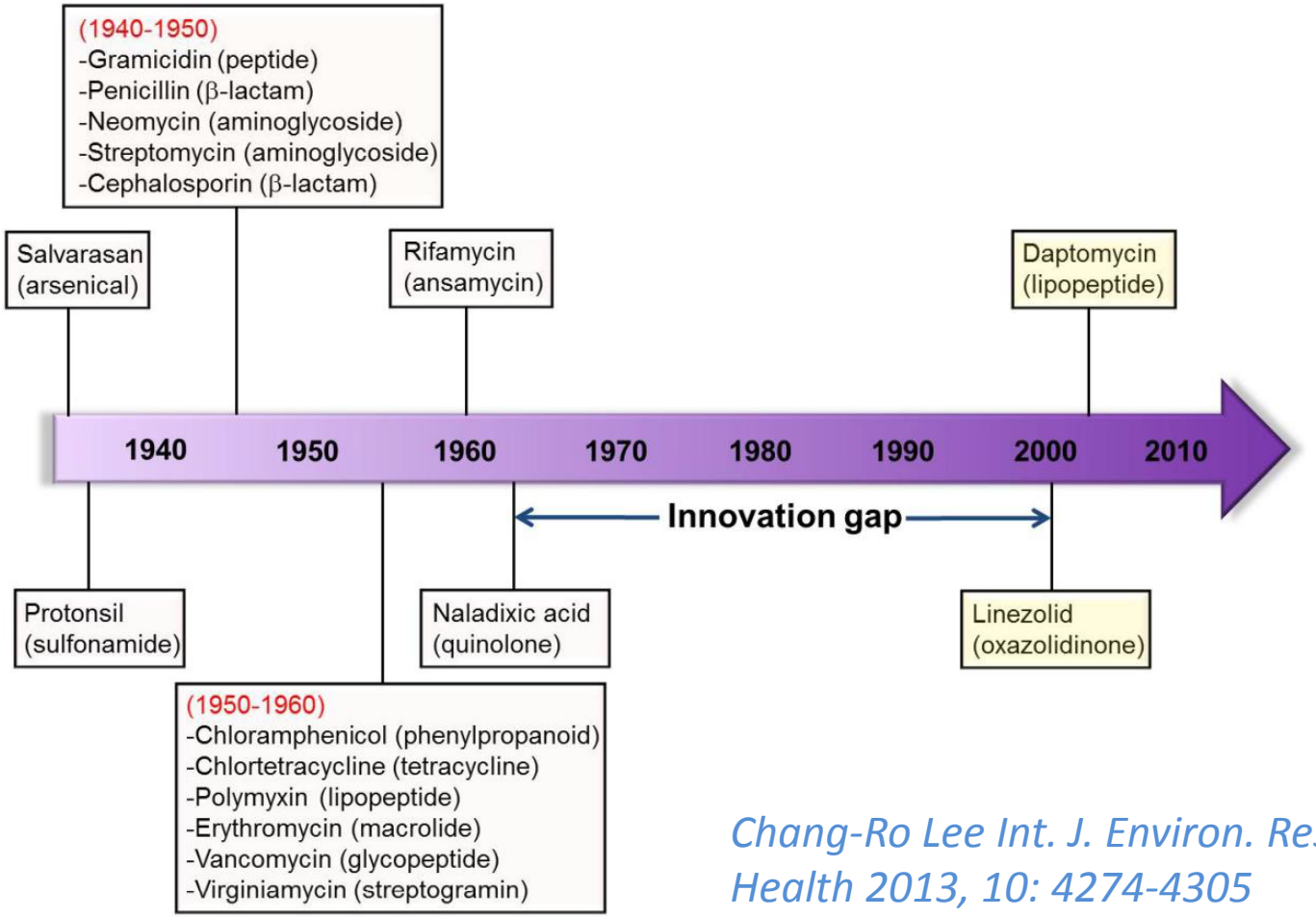
Inicio
Era Antibiótica

En 1928, el investigador Alexander Fleming descubrió la penicilina, un acontecimiento que cambiaría el curso de la historia de la Medicina. Este hallazgo, abrió las puertas de la revolución antibiótica. Fleming comunicó su descubrimiento sobre la penicilina en el British Journal of Experimental Pathology en 1929. Por sus descubrimientos Fleming compartió el Premio Nobel en 1945 junto a E.BorisChain y H.W.Florey.

Era antibiótica

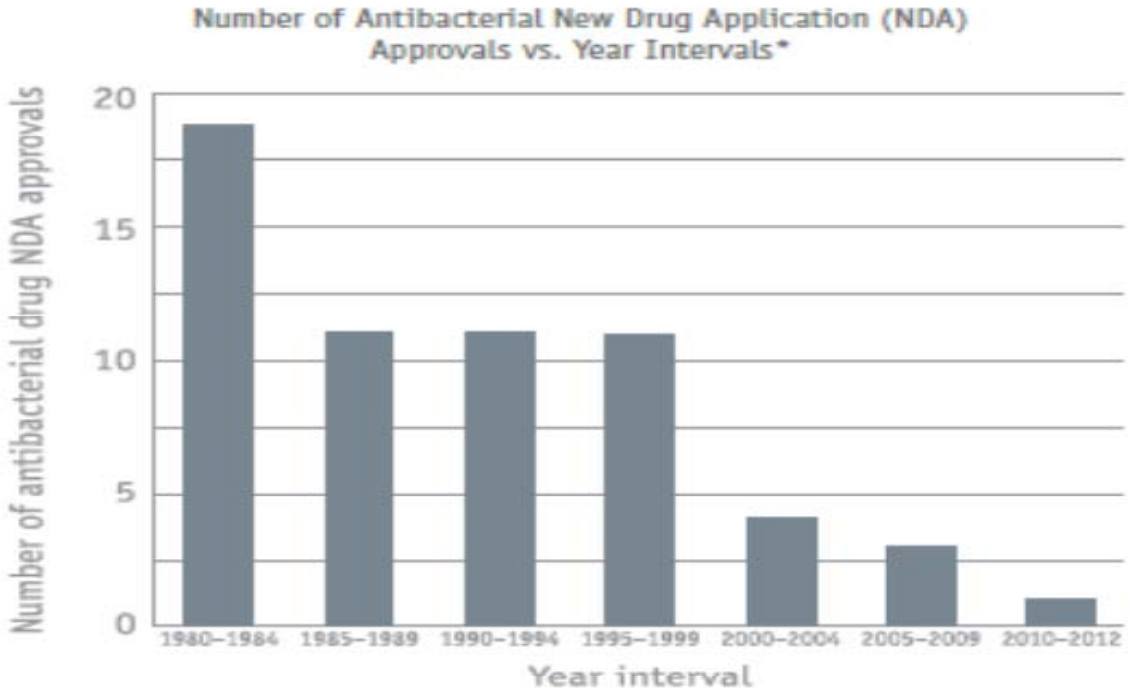
- El tto. AB supuso un cambio de curso de la medicina tradicional: las infecciones y plagas dejaron de ser el > problema de salud, aumentando la esperanza de vida y disminuyendo la mortalidad
- Permitió el desarrollo de procedimientos asociados a alta probabilidad de infecciones graves: trasplantes, ventilación mecánica, Q..
- Sensación de éxito y control de las enfermedades infecciosas

Desarrollo AB



Chang-Ro Lee Int. J. Environ. Res. Public Health 2013, 10: 4274-4305

Políticas de incentivación desarrollo de nuevos antibacterianos



*Intervals from 1980–2009 are 5-year intervals; 2010–2012 is a 3-year interval. Drugs are limited to systemic agents.
Data courtesy of FDA's Center for Drug Evaluation and Research (CDER).

AB, microbiosfera y R

- Introducción AB: >intervención humana en la microbiosfera
- Producción mundial AB:

  100.000-200.000 ton/año: ½ uso no-humano
- Potencial para alterar la estructura genética microbiana global: caos en el ecosistema bacteriano
- Prevalencia de resistencias microbianas en ecosistemas no-clínicos

Uso y abuso de AB en ámbitos no-clínicos

- En veterinaria: bajas dosis en largos periodos, en alimentos animales de granja(avoparcina)
- En aquacultura: AB han generado plásmidos MDR transferibles (de *Aeromonas salmonicida* a *E. coli)*
- En apicultura (tetraciclinas >50 años)
- En agricultura: uso masivo (cultivo orquídeas)

AISLAMIENTO DE HONGOS MICORRICICOS DE RAIZ DE ORQUÍDEAS ORIGINARIAS DEL SOCONUSCO, CHIAPAS.

Munguía Fragozo P. V[1]., Gómez Sumuano S[2]., Olalde Portugal V[2].

1. Universidad Autónoma de Querétaro
2. Centro de Investigación y Estudios Avanzados del IPN (CINVESTAV), Campus Irapuato.

RESUMEN.

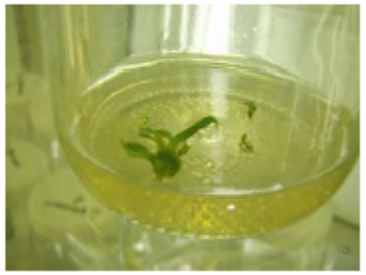
Se realizó el cultivo y aislamiento de hongos micorriza provenientes de raíz de orquídea, la germinación de semillas en diferentes condiciones del medio de cultivo y el sub cultivo de las plántulas de orquídea a diferentes condiciones de medio para determinar el sustrato óptimo para el crecimiento y desarrollo de las orquídeas y establecer de esta manera la mejor estrategia de propagación de las plantas para evitar la extinción de estas especies amenazadas y de esta manera promover la renovación de su hábitat que se encuentra amenazado por la actividad humana.

Preparación del medio MS para germinación de semillas de orquídea.

Fórmula para medio Murashige y Skoog (1962) El medio se preparó a partir de los stocks A, B, C, D, E, F y G en un litro de agua destilada y se añadió 9 g/L de agar bacteriológico (Sigma) y se reguló el pH a 5.7

Se establecieron dos condiciones de germinación:

- la normal y
- la adicionada con antibióticos y hormonas de crecimiento.
  - Ácido Giberélico (Sigma)
  - Benziladenina (J.T. Baker Co.)
  - Ampicilina 25 µg/L.
  - Streptomicina 25 µg/L
  - Rifampicina 6 µg/L
  - Cefotaxima 25 µg/L



AB utilizados en alimentación ganadería

Antimicrobial Drugs Approved for Use in Food-Producing Animals: 2009 Sales and Distribution Data Reported by Drug Class

drug class	Kilograms	pounds	% of total
FOOD-ANIMAL USE			
aminoglycosides	339,678	748,862	2%
cephalosporins	41,328	91,113	0%
ionophores	3,740,627	8,246,671	23%
lincosamides	115,837	255,377	1%
macrolides	861,985	1,900,352	5%
penicillins	610,514	1,345,953	4%
sulfas	517,873	1,141,715	3%
tetracyline	4,611,892	10,167,481	28%
NIR	2,227,366	4,910,501	14%
sub-total	13,067,100	28,808,024	**79.8%**
HUMAN MED USE	3,300,000	7,275,255	**20.2%**
TOTAL	16,367,100	36,083,279	100%

Source: FDA

Preserving Antibiotics, Rationally

Aidan Hollis, Ph.D., and Ziana Ahmed, B.A.Sc.

N ENGL J MED 369;26 NEJM.ORG DECEMBER 26, 2013

51Ton AB consumidos diariamente en US:
80% EN AGRICULTURA, AQUACULTURA Y GANADERÍA y a niveles subterapéuticos

<u>Recomendaciones realizadas en US (FDA):</u>
- 2005: Evitar uso de FQ en avicultura
- 2012: Evitar uso para favorecer crecimiento
- 2013: Recomendación a la industria farmacéutica de disminuir la producción

<u>Recomendaciones en EU</u>: Prohibición uso AB para engorde en ganadería:
- 1986 en Suecia, seguida de Dinamarca
- 2005: extensión a EU.

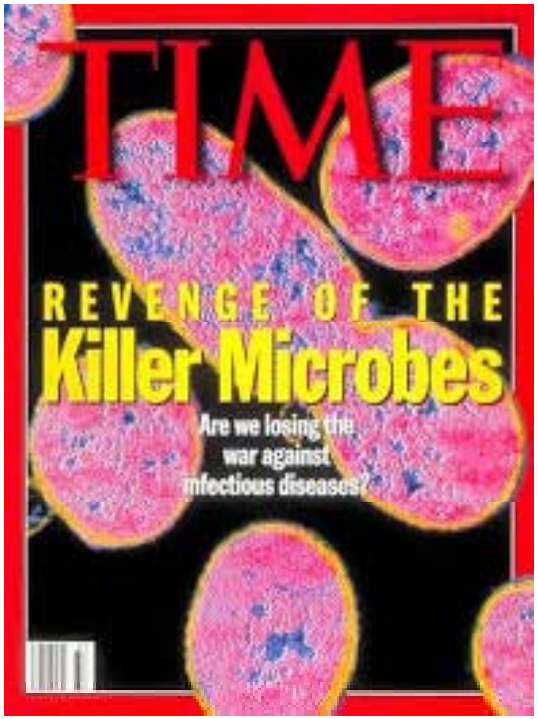
PROPUESTA DE LOS AUTORES:
Limitar el uso en cuanto a cantidad, mediante pago de tasas

Efectos AB en la microbiosfera

- E. predecibles: R antibiótica con modificaciones genéticas, algunas irreversibles.

- E. impredecibles: modificación interacciones entre microbiosfera y animales, plantas y sus ciclos vitales, con repercusión en las condiciones ambientales del planeta.

Principio del Fin



Sep. 12, 1994

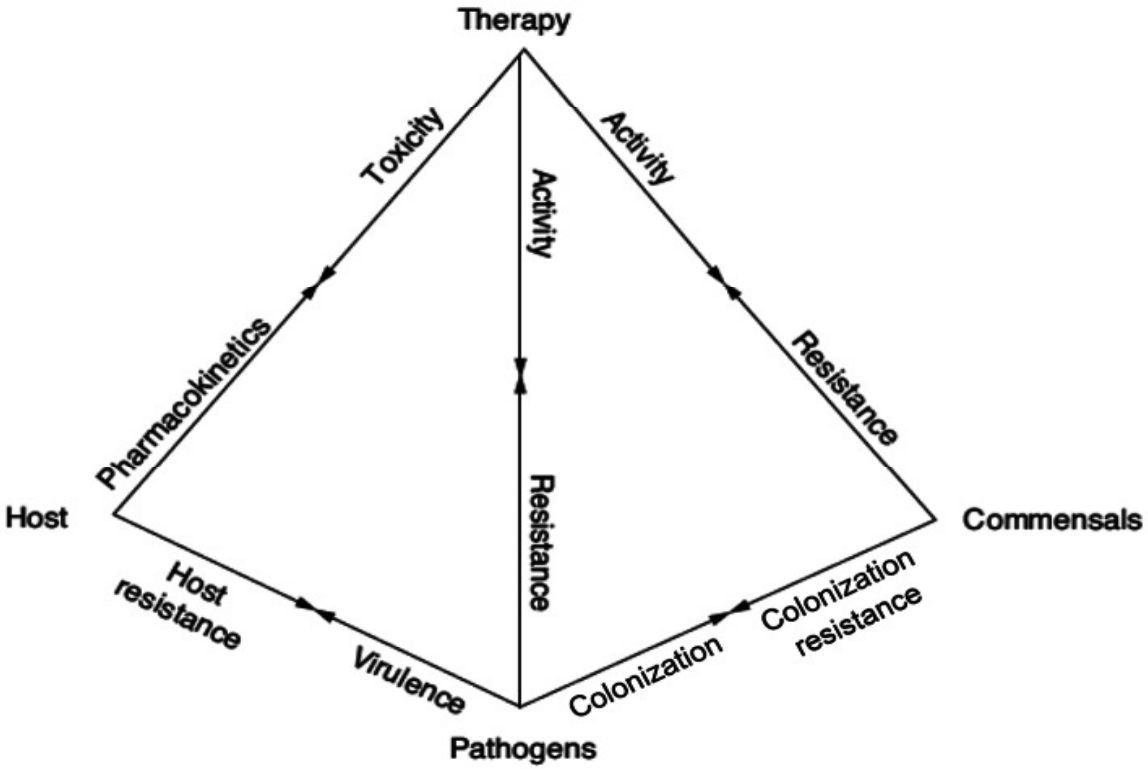
Doctors and the public were not alone in feeling cocky about infectious disease a decade ago. The drug companies did too. **More than 100 antibiotics were on the market, and they had most bacterial diseases on the run, if not on the verge of eradication.** So rosy was the outlook that **U.S. government funding & for antibiotic research was declining**, and many pharmaceutical firms were focusing on cancer and viral diseases, especially AIDS.

Situación actual:
Emergencia y expansión R a AB:

- Más de 40 años de alarma
- 25000 fallecimientos anuales atribuibles en EU
- 23000 fallecimientos anuales atribuibles en US

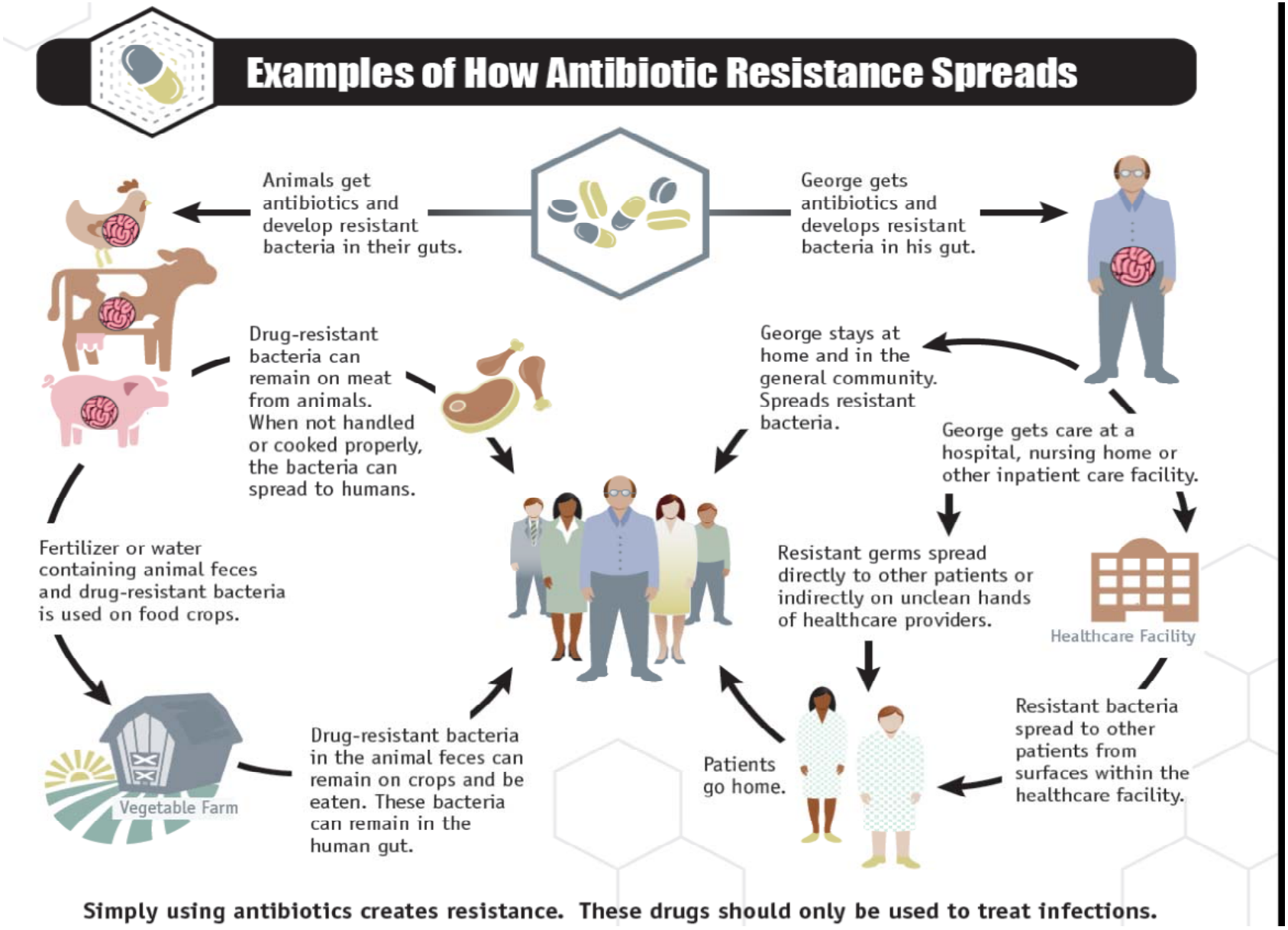
Qué ocurre?, Por qué nada cambia?

Interacciones: AB, paciente, patógenos y microflora



El coste de la actividad antimicrobiana es el desarrollo de AB-R por el patógeno y por la microbiota colonizante.

Examples of How Antibiotic Resistance Spreads



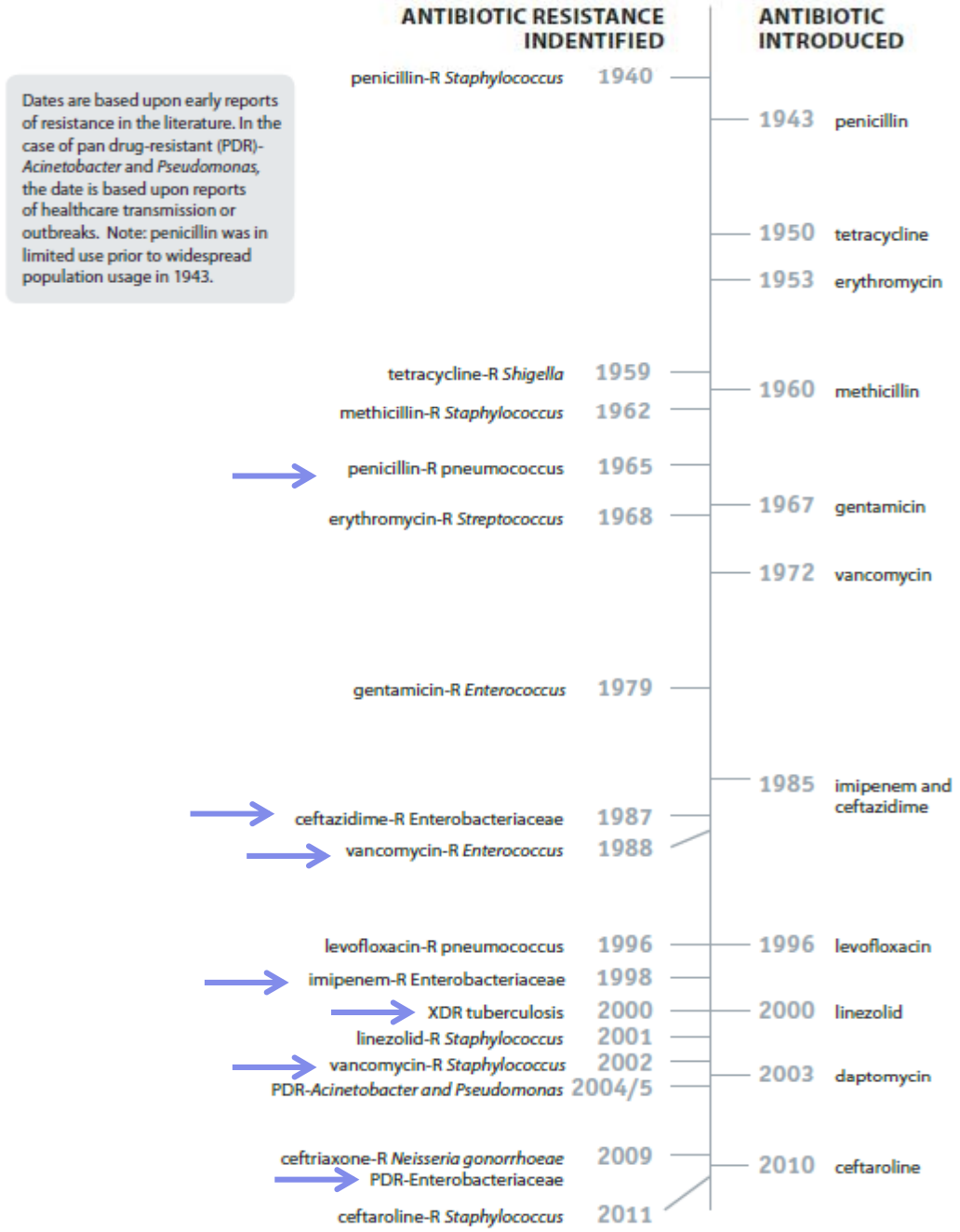
Simply using antibiotics creates resistance. These drugs should only be used to treat infections.

Principales patógenos resistentes

- **Bacterias (adquiridas en el medio extrahospitalario)**
- *Escherichia coli*
- *Mycobacterium tuberculosis* (causante de la tuberculosis)
- *Neisseria gonorrhoeae* (causante de la gonorrea)
- *Salmonella typhi*
- *Staphylococcus aureus,* incluidas las cepas resistentes a la meticilina adquiridas en el medio extrahospitalario
- *Streptococcus pneumoniae*
- **Bacterias (adquiridas en el medio hospitalario)**
- *Acinetobacter baumannii*
- *Enterococcus faecium y Enterococcus faecalis,* incluidas las cepas resistentes a la vancomicina
- Patógenos entéricos multirresistentes, entre ellos *Escherichia coli y Klebsiella pneumoniae* productoras de las enzimas ESBL y KPC
- *Pseudomonas aeruginosa*
- *Staphylococcus aureus,* incluidas las cepas resistentes a la meticilina
- *Stenotrophomonas maltophilia*
- **Bacterias (enfermedades zoonóticas)**
- *Campylobacter* spp.
- *Salmonella* spp.

Developing Resistance

Timeline of Key Antibiotic Resistance Events

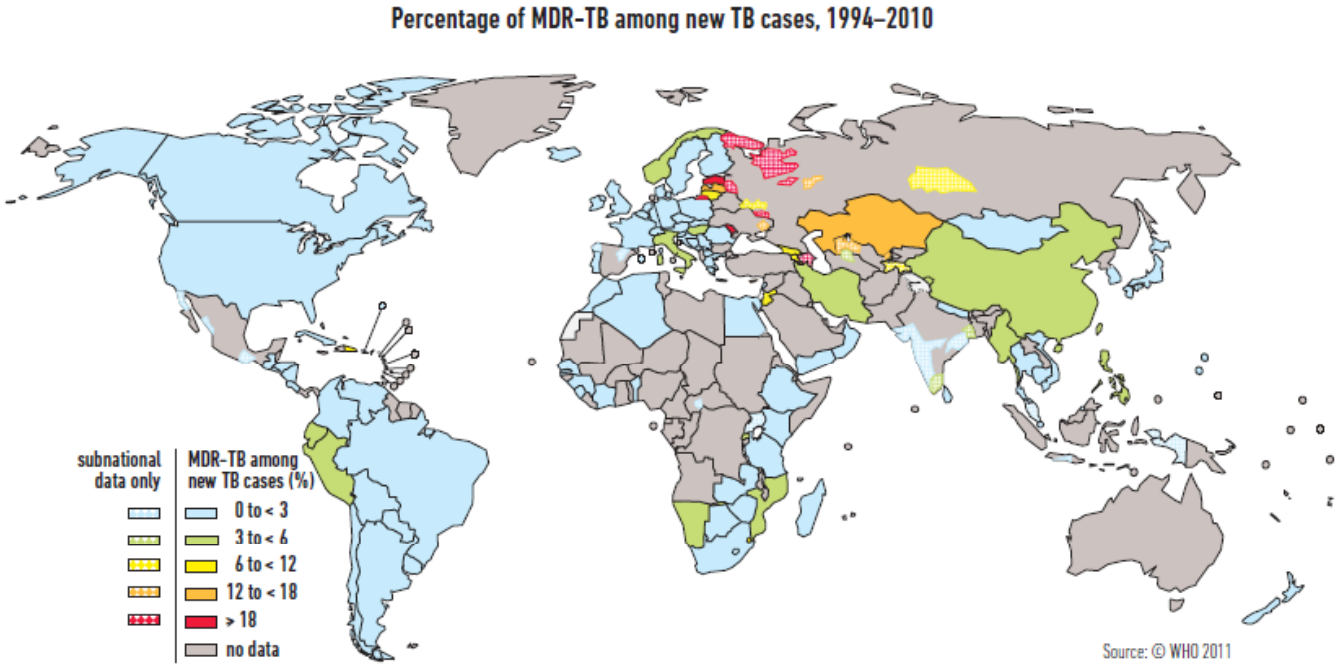


Desarrollo de R

Tbc-MDR 1994-2010

MULTIDRUG-RESISTANT TB

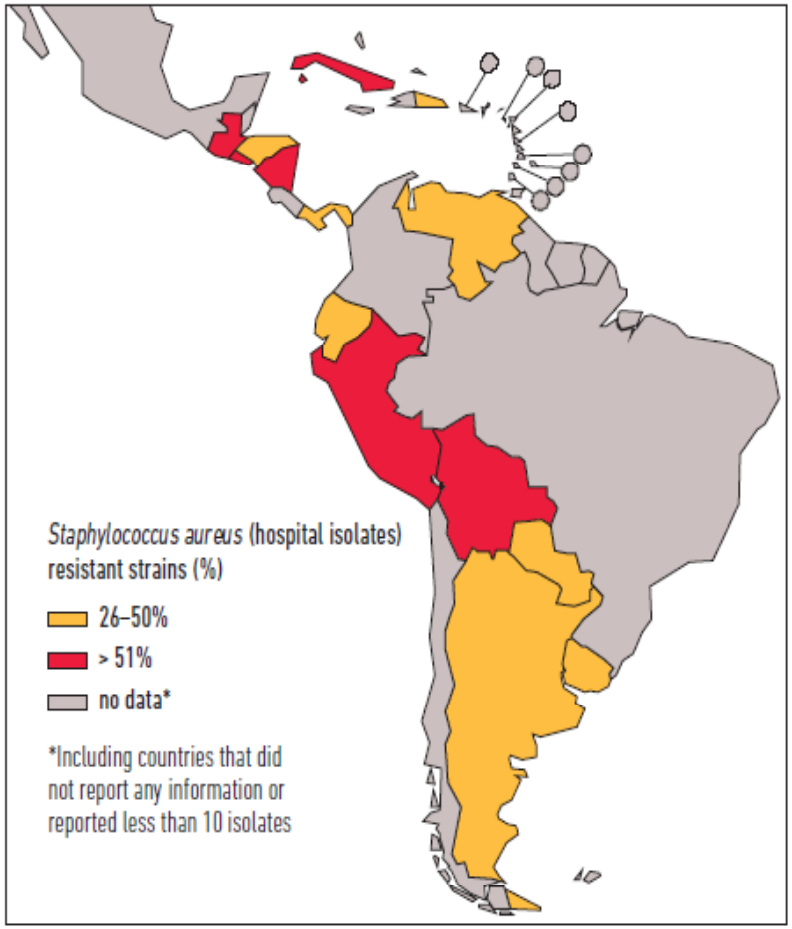
Globally in 2012, an estimated **450 000 people developed multidrug-resistant TB (MDR-TB)** and there were an estimated **170 000 deaths from MDR-TB**.



World Health Organization

MRSA nosocomial 2007

Staphylococcus aureus (hospital isolates): percentage of methicillin-resistant strains, 2007, Latin America and the Caribbean



Adapted from: *Annual report on the antibiotic resistance monitoring/surveillance network, 2008*

Source: Latin American Resistance Surveillance Network, 2007. © PAHO HSD/CD 2011

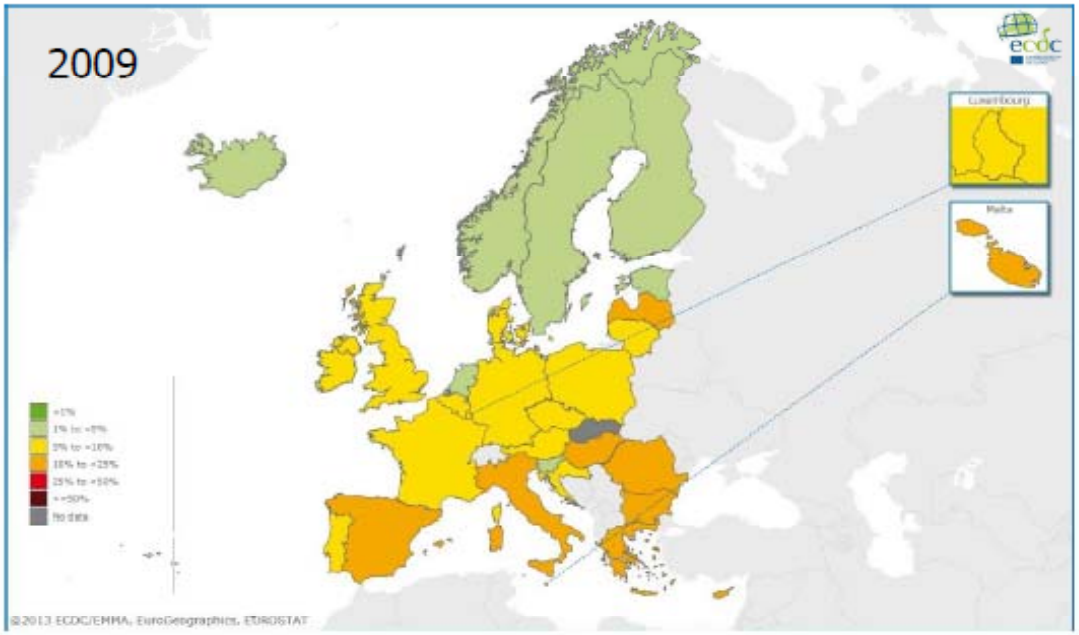
Summary of the latest data on antibiotic resistance in the European Union

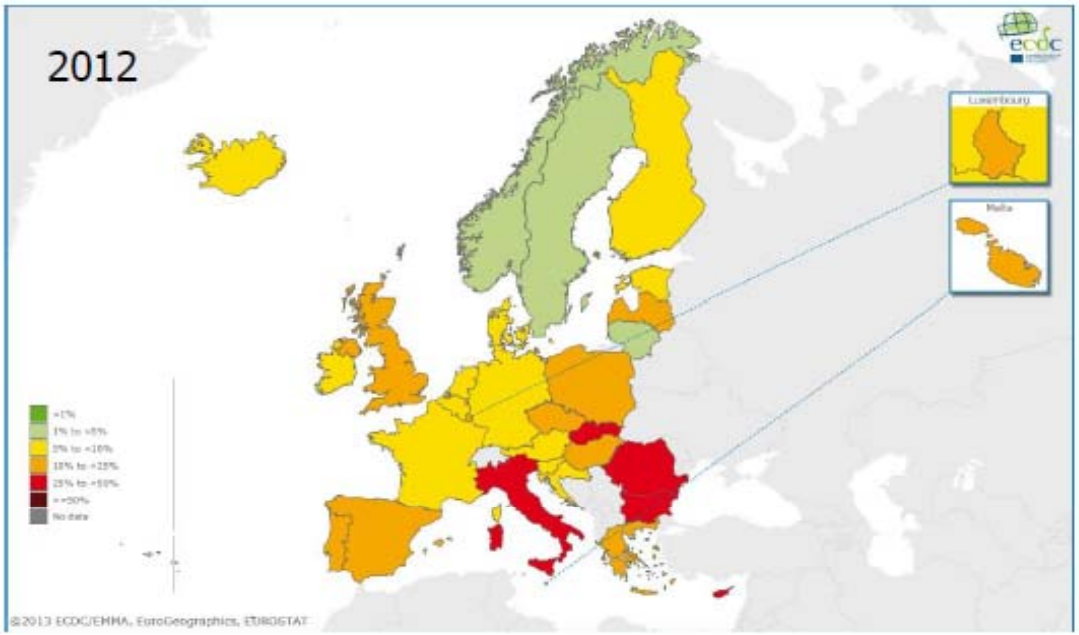
November 2013

Highlights on antibiotic resistance

- Antibiotic resistance is a serious threat to public health in Europe, leading to increasing healthcare costs, prolonged hospital stays, treatment failures, and sometimes death.
- Over the last four years (2009 to 2012), resistance to third-generation cephalosporins in *K. pneumoniae* and *E. coli* increased significantly at EU/EEA level. Combined resistance to third-generation cephalosporins and two other important antimicrobial groups (fluoroquinolones and aminoglycosides) also increased significantly at EU/EEA level for *K. pneumoniae*, but not for *E. coli*.
- The increasing trend of combined resistance in *K. pneumoniae* means that only a few therapeutic options (e.g., carbapenems) remain available for treatment of infected patients.
- Carbapenems form a major last-line class of antibiotics to treat infections with multidrug-resistant Gram-negative bacteria such as *K. pneumoniae* and *E. coli*, both common causes of pneumonia, urinary tract infections and bloodstream infections. However, the percentage of carbapenem-resistant *K. pneumoniae* is already high and increasing in some countries in the EU.
- Antimicrobial resistance data for *Acinetobacter* spp. are available in EARS-Net for the first time. Data for 2012 show large inter-country variations in Europe, and high levels of resistance (>25%) to carbapenems in nearly half of the reporting countries.
- In contrast, in the past few years, the percentage of meticillin-resistant *Staphylococcus aureus* (MRSA) has shown a significant decreasing trend at EU/EEA level, and either a continuous decrease or a stabilising trend was observed in most EU/EEA countries during the last four years. Nevertheless, MRSA remains above 25% in almost one fourth of the reporting countries, mainly in southern and eastern Europe.
- Prudent antibiotic use and comprehensive infection control strategies targeting all healthcare sectors (acute care hospitals, long-term care facilities and ambulatory care) are the cornerstones of effective interventions that aim to prevent selection and transmission of antibiotic-resistant bacteria.

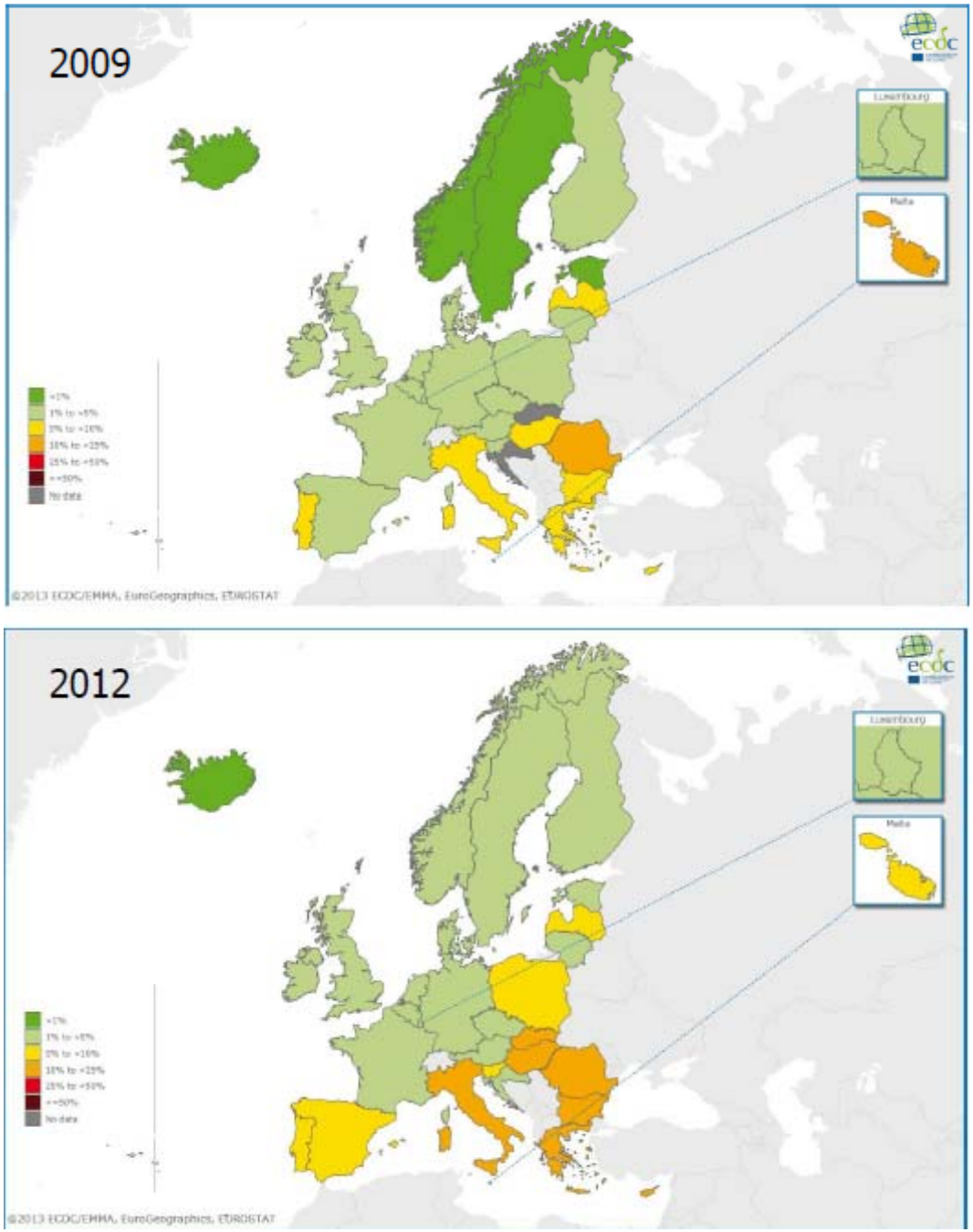
Figure 3. *Escherichia coli*: percentage of invasive isolates with resistance to third-generation cephalosporins, EU/EEA, 2009 (top) and 2012 (bottom)





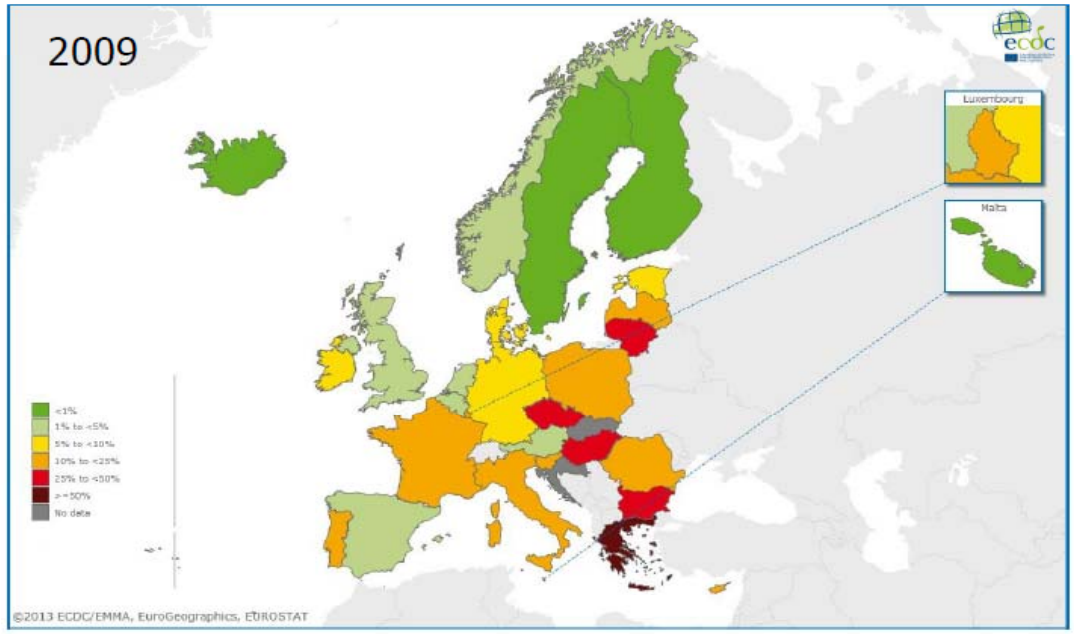
E. Coli
Cefalosp 3ªG- R

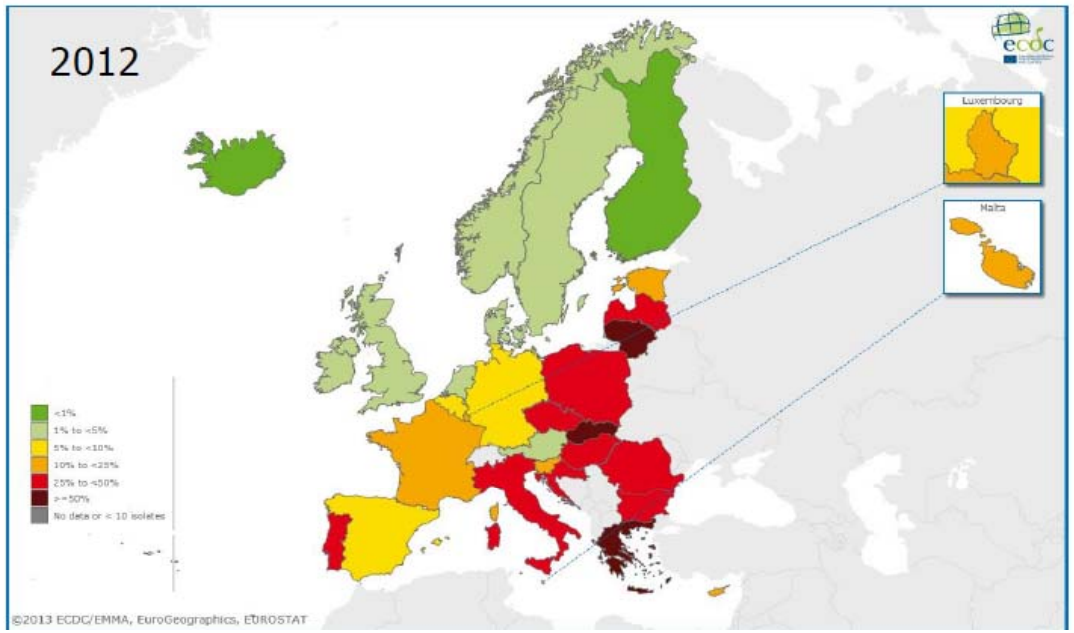
Figure 4. *Escherichia coli:* percentage of invasive isolates with combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides, EU/EEA, 2009 (top) and 2012 (bottom)



E. coli
(3ªG-cef+FQ+ AG)-R

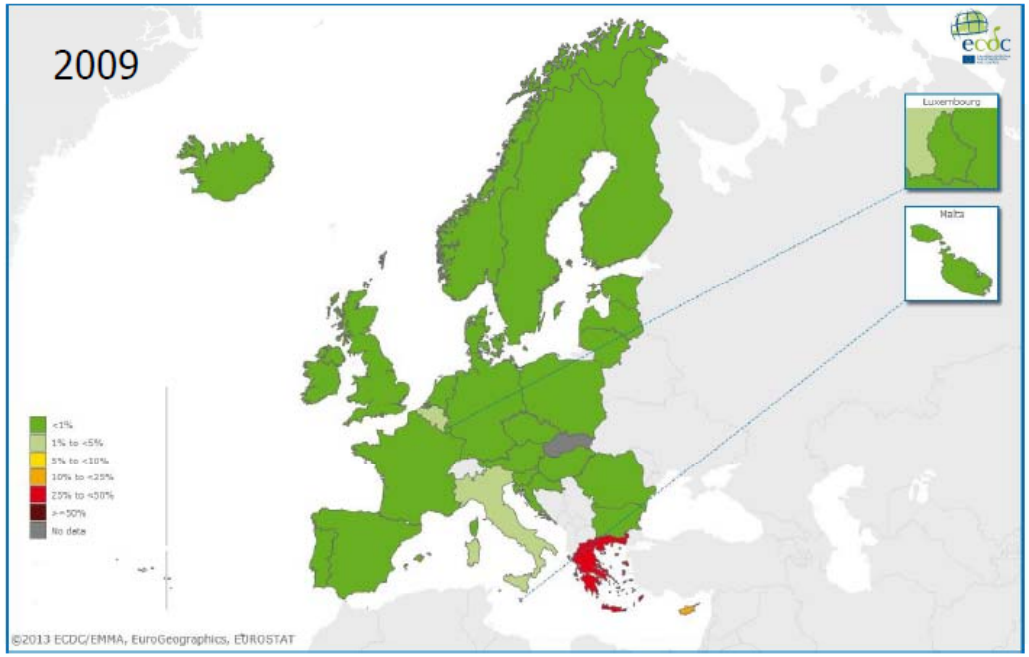
Figure 1. ***Klebsiella pneumoniae*: percentage of invasive isolates with combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides, EU/EEA, 2009 (top) and 2012 (bottom)**

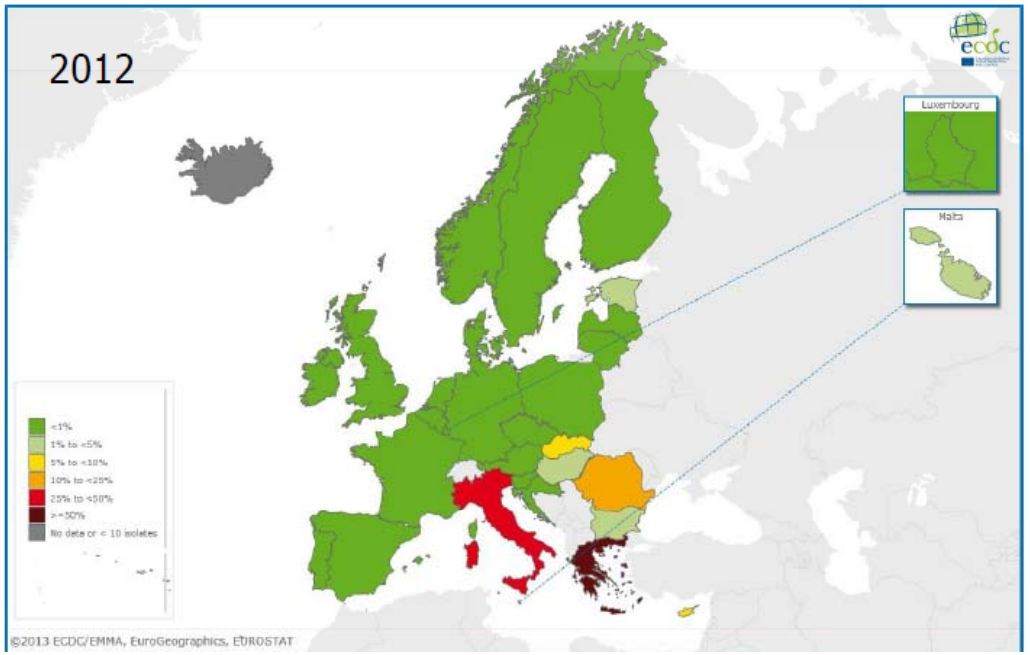




K. pneumoniae
(3ªG-cef+FQ+AG)-R

Figure 2. *Klebsiella pneumoniae*: percentage of invasive isolates with resistance to carbapenems, EU/EE
2009 (top) and 2012 (bottom)

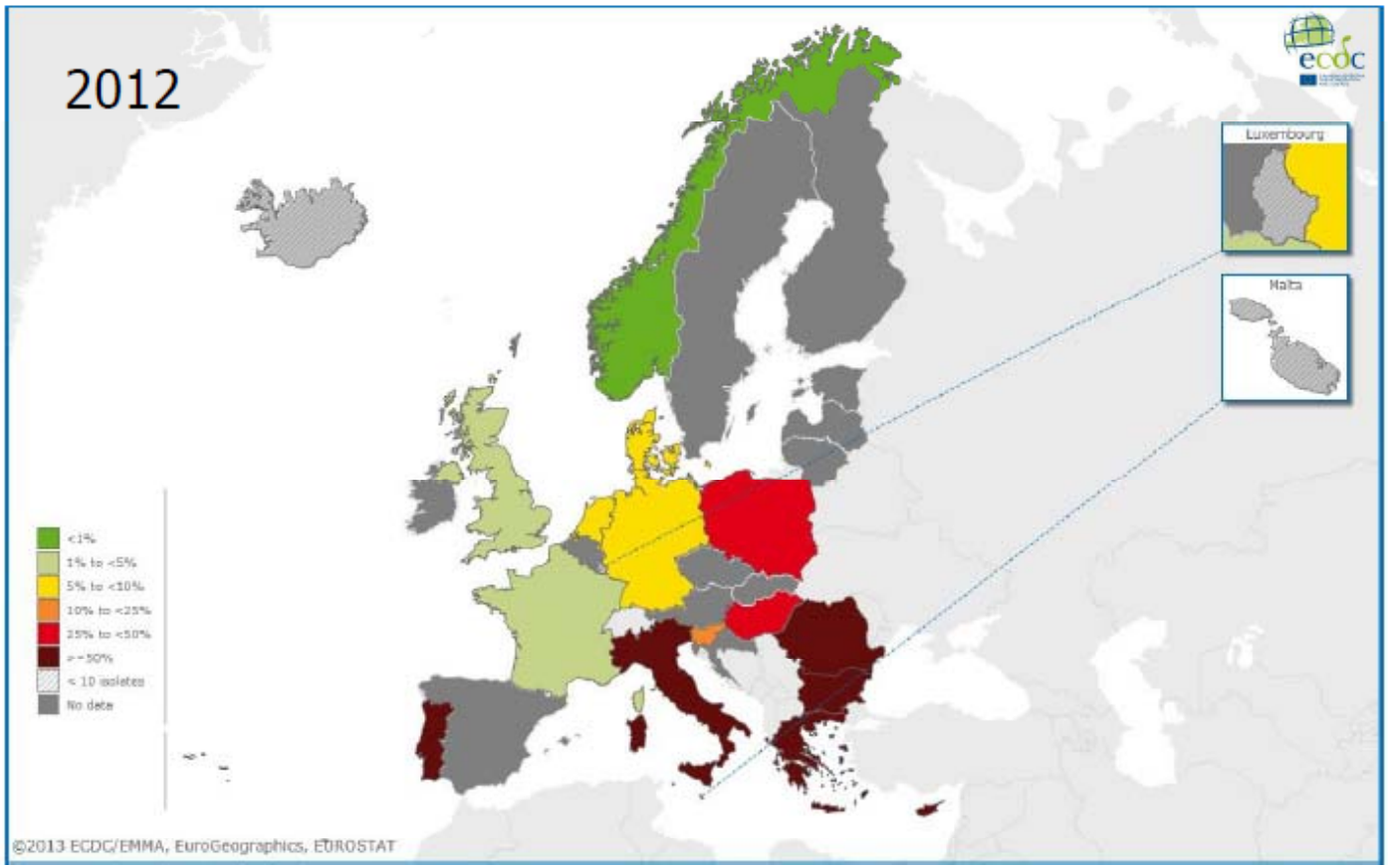




K. pneumoniae
carbapenem-R

Acinetobacter sp: carbapenem-R

Figure 5. *Acinetobacter* species: percentage of invasive isolates with resistance to carbapenems, EU/EEA, 2012



Prioridades de control de infecciones MDR

HAZARD LEVEL
URGENT

These are high-consequence antibiotic-resistant threats because of significant risks identified across several criteria. These threats may not be currently widespread but have the potential to become so and require urgent public health attention to identify infections and to limit transmission.

Clostridium difficile (C. difficile), Carbapenem-resistant Enterobacteriaceae (CRE), Drug-resistant *Neisseria gonorrhoeae* (cephalosporin resistance)

HAZARD LEVEL
SERIOUS

These are significant antibiotic-resistant threats. For varying reasons (e.g., low or declining domestic incidence or reasonable availability of therapeutic agents), they are not considered urgent, but these threats will worsen and may become urgent without ongoing public health monitoring and prevention activities.

Multidrug-resistant *Acinetobacter,* Drug-resistant *Campylobacter,* Fluconazole-resistant *Candida* (a fungus), Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs), Vancomycin-resistant *Enterococcus* (VRE), Multidrug-resistant *Pseudomonas aeruginosa,* Drug-resistant Non-typhoidal *Salmonella,* Drug-resistant *Salmonella* Typhi, Drug-resistant *Shigella,* Methicillin-resistant *Staphylococcus aureus* (MRSA), Drug-resistant *Streptococcus pneumonia,* Drug-resistant tuberculosis (MDR and XDR)

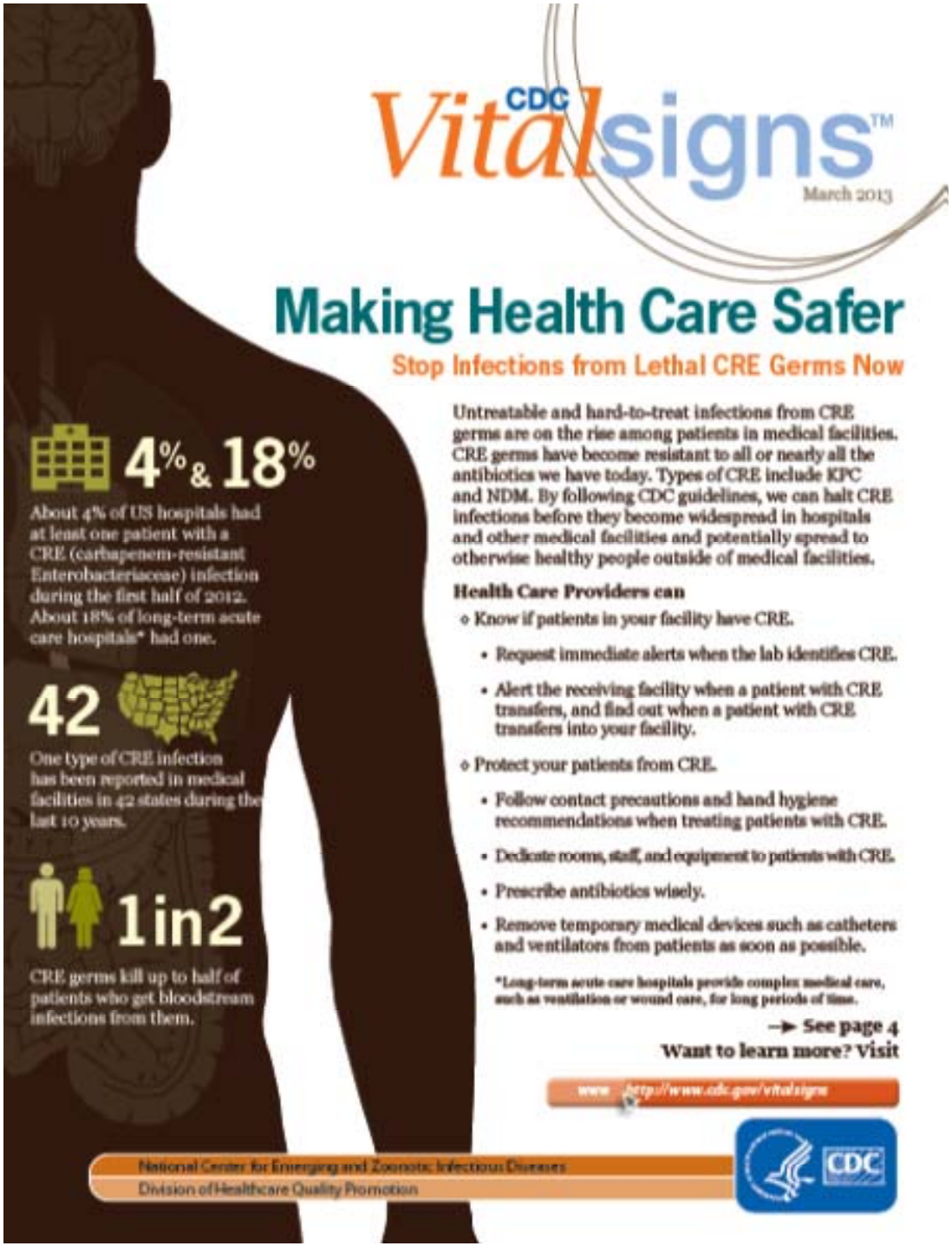
HAZARD LEVEL
CONCERNING

These are bacteria for which the threat of antibiotic resistance is low, and/or there are multiple therapeutic options for resistant infections. These bacterial pathogens cause severe illness. Threats in this category require monitoring and in some cases rapid incident or outbreak response.

Vancomycin-resistant *Staphylococcus aureus* (VRSA), Erythromycin-resistant *Streptococcus* Group A, Clindamycin-resistant *Streptococcus* Group B

Although *C. difficile* is not currently significantly resistant to antibiotics used to treat it, it was included in the threat assessment because of its unique relationship with resistance issues, antibiotic use, and its high morbidity and mortality.

Enterobacterias Carbapenem-R



CDC Vitalsigns™

March 2013

Making Health Care Safer

Stop Infections from Lethal CRE Germs Now

4% & 18%

About 4% of US hospitals had at least one patient with a CRE (carbapenem-resistant Enterobacteriaceae) infection during the first half of 2012. About 18% of long-term acute care hospitals* had one.

42

One type of CRE infection has been reported in medical facilities in 42 states during the last 10 years.

1 in 2

CRE germs kill up to half of patients who get bloodstream infections from them.

Untreatable and hard-to-treat infections from CRE germs are on the rise among patients in medical facilities. CRE germs have become resistant to all or nearly all the antibiotics we have today. Types of CRE include KPC and NDM. By following CDC guidelines, we can halt CRE infections before they become widespread in hospitals and other medical facilities and potentially spread to otherwise healthy people outside of medical facilities.

Health Care Providers can

- Know if patients in your facility have CRE.
  - Request immediate alerts when the lab identifies CRE.
  - Alert the receiving facility when a patient with CRE transfers, and find out when a patient with CRE transfers into your facility.
- Protect your patients from CRE.
  - Follow contact precautions and hand hygiene recommendations when treating patients with CRE.
  - Dedicate rooms, staff, and equipment to patients with CRE.
  - Prescribe antibiotics wisely.
  - Remove temporary medical devices such as catheters and ventilators from patients as soon as possible.

*Long-term acute care hospitals provide complex medical care, such as ventilation or wound care, for long periods of time.

→ See page 4

Want to learn more? Visit

www.http://www.cdc.gov/vitalsigns

National Center for Emerging and Zoonotic Infectious Diseases
Division of Healthcare Quality Promotion

CDC

Action is needed now to stop these deadly infections.

Problem

CRE germs have found ways to beat antibiotics.

- CRE infections are caused by a family of germs that are a normal part of a person's healthy digestive system. These germs can cause infections when they get into the bladder, blood, or other areas where germs don't belong.
- Some of these germs have become resistant to all or almost all antibiotics, including last-resort drugs called carbapenems. These resistant germs are called CRE.
- Almost all CRE infections happen to patients receiving serious medical care. CRE infections are hard to treat, and in some cases, untreatable. CRE kill up to half of patients who get bloodstream infections from them.
- In addition to spreading among people, CRE easily spread their antibiotic resistance to other kinds of germs, making those potentially untreatable as well.

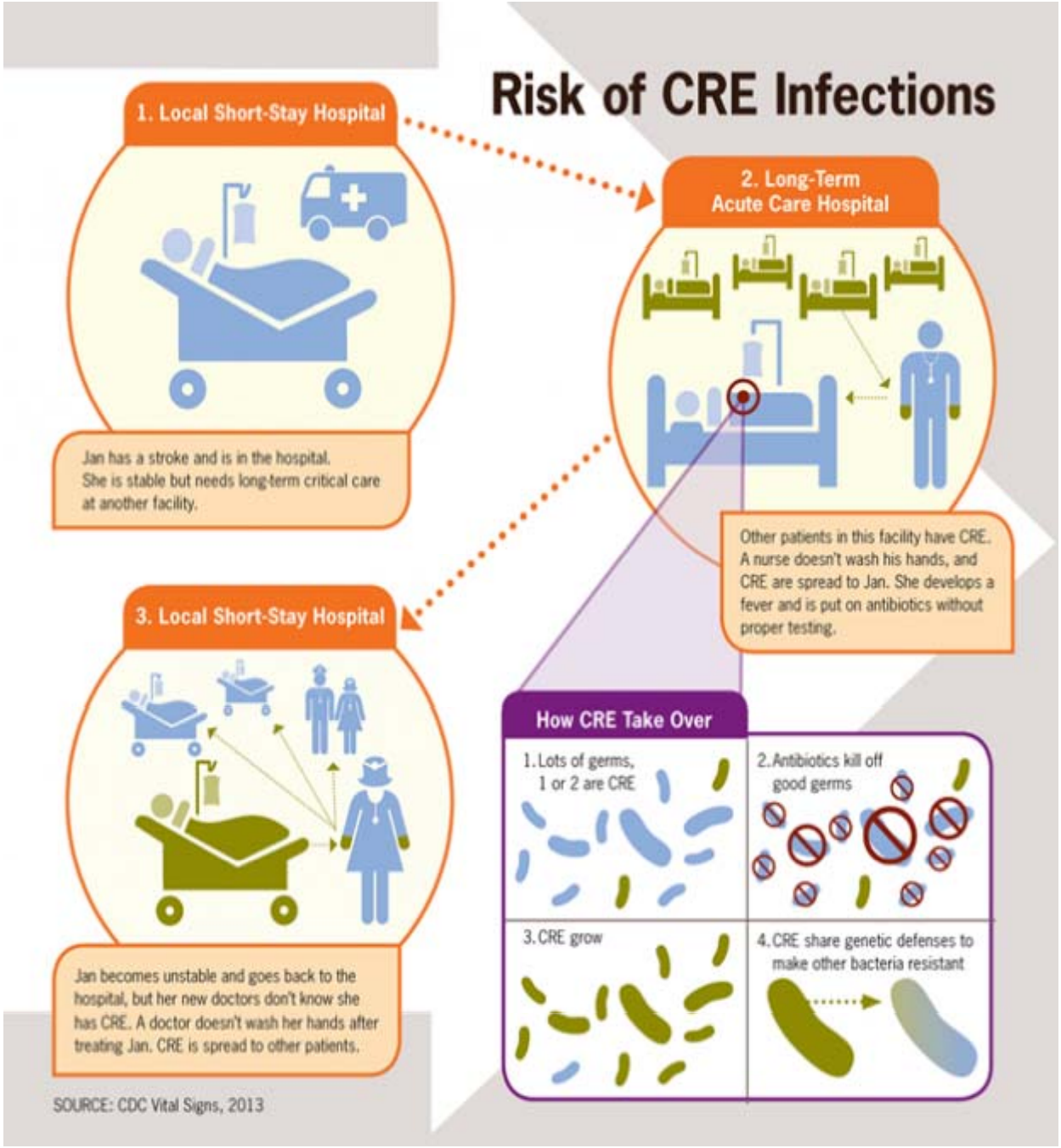
CRE infections are spreading, and urgent action is needed to stop them.

- Although CRE germs are not very common, they have increased from 1% to 4% in the past decade. One type of CRE has increased from 2% to 10%.
- CRE are more common in some US regions, such as the Northeast, but 42 states report having had at least one patient test positive for one type of CRE.
- About 18% of long-term acute care hospitals and about 4% of short-stay hospitals in the US had at least one CRE infection during the first half of 2012.
- CRE's ability to spread themselves and their resistance raises the concern that potentially untreatable infections could appear in otherwise healthy people.

CRE infections can be prevented.

- Medical facilities in several states have reduced CRE infection rates by following CDC's prevention guidelines (see box).
- Israel decreased CRE infection rates in all 27 of its hospitals by more than 70% in one year with a coordinated prevention program.
- The US is at a critical time in which CRE infections could be controlled if addressed in a rapid, coordinated, and consistent effort by doctors, nurses, lab staff, medical facility leadership, health departments/states, policy makers, and the federal government.

CDC's 2012 CRE Toolkit provides CRE prevention guidelines for doctors and nurses, hospitals, long-term acute care hospitals, nursing homes, and health departments. It gives step-by-step instructions for facilities treating patients with CRE infections and for those not yet affected by them. (http://www.cdc.gov/hai/organisms/cre/cre-toolkit/index.html)

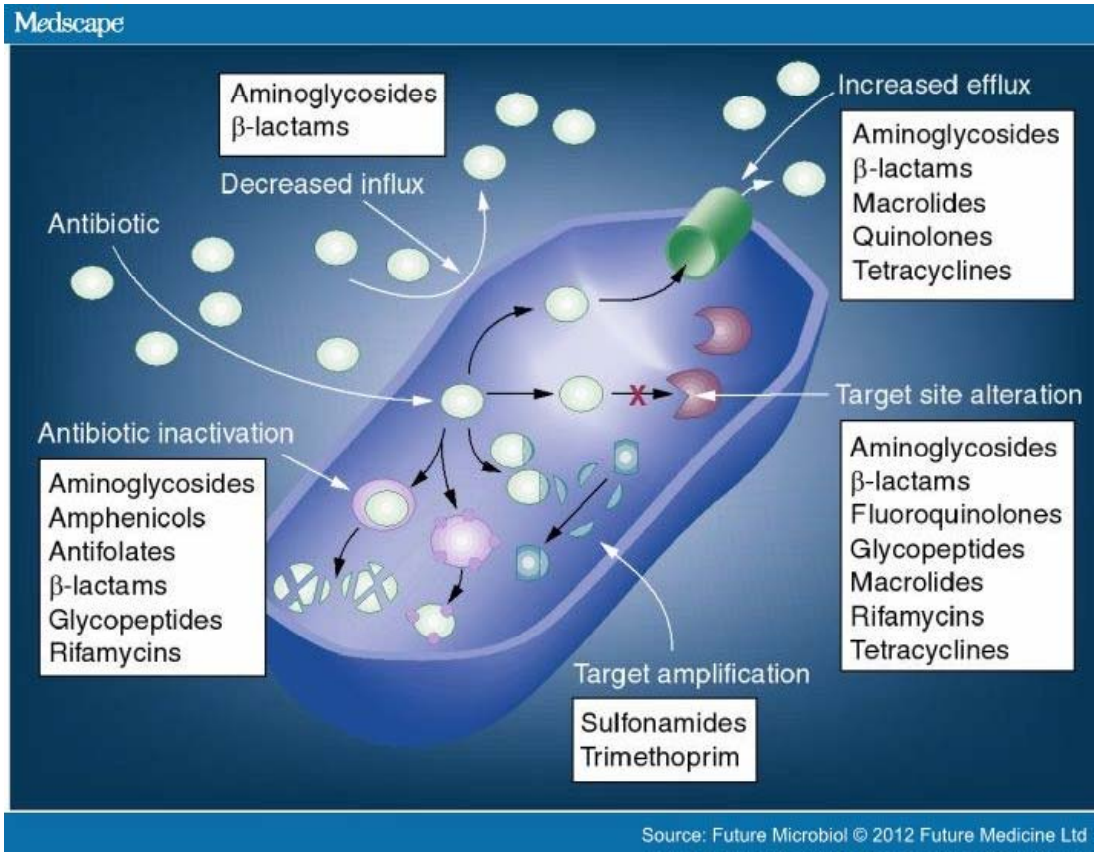

Risk of CRE Infections
1. Local Short-Stay Hospital
Jan has a stroke and is in the hospital. She is stable but needs long-term critical care at another facility.
2. Long-Term Acute Care Hospital
Other patients in this facility have CRE. A nurse doesn't wash his hands, and CRE are spread to Jan. She develops a fever and is put on antibiotics without proper testing.
3. Local Short-Stay Hospital
Jan becomes unstable and goes back to the hospital, but her new doctors don't know she has CRE. A doctor doesn't wash her hands after treating Jan. CRE is spread to other patients.
How CRE Take Over
1. Lots of germs, 1 or 2 are CRE
2. Antibiotics kill off good germs
3. CRE grow
4. CRE share genetic defenses to make other bacteria resistant
SOURCE: CDC Vital Signs, 2013

Conceptos de AB-R

- Clínico: puntos de corte de Con AB asociadas a fracaso terapéutico. Establecidos por CLSI y EUCAST
- Microbiológico: presencia de mecanismos de R que reducen su sensibilidad respecto a las cepas salvajes.

- AB-R microbiológica de bajo nivel es preludio de R clínica

Mecanismos de AB-R intrínseca



- Inactivación o modificación del AB
- Alteración del sitio diana del AB que reduce su capacidad de unión.
- Modificación de los patrones metabólicos para anular el efecto AB
- Reducción del depósito intracelular de AB, disminuyendo la permeabilidad y/o aumentando el eflujo activo de AB.

Mecanismos de adquisición de R y factores determinantes

1. Selección de mutaciones cromosómicas

- Presión AB

2. Adquisición de determinantes de R por transferencia horizontal
3. Diseminación clonal de cepas R

- Epidemiología local
- Grado de contaminación ambiental
- Posibilidad transmisión: hacinamiento, politica control infecc.

Exposición AB (PK/PD) y Selección de mutaciones cromosómicas

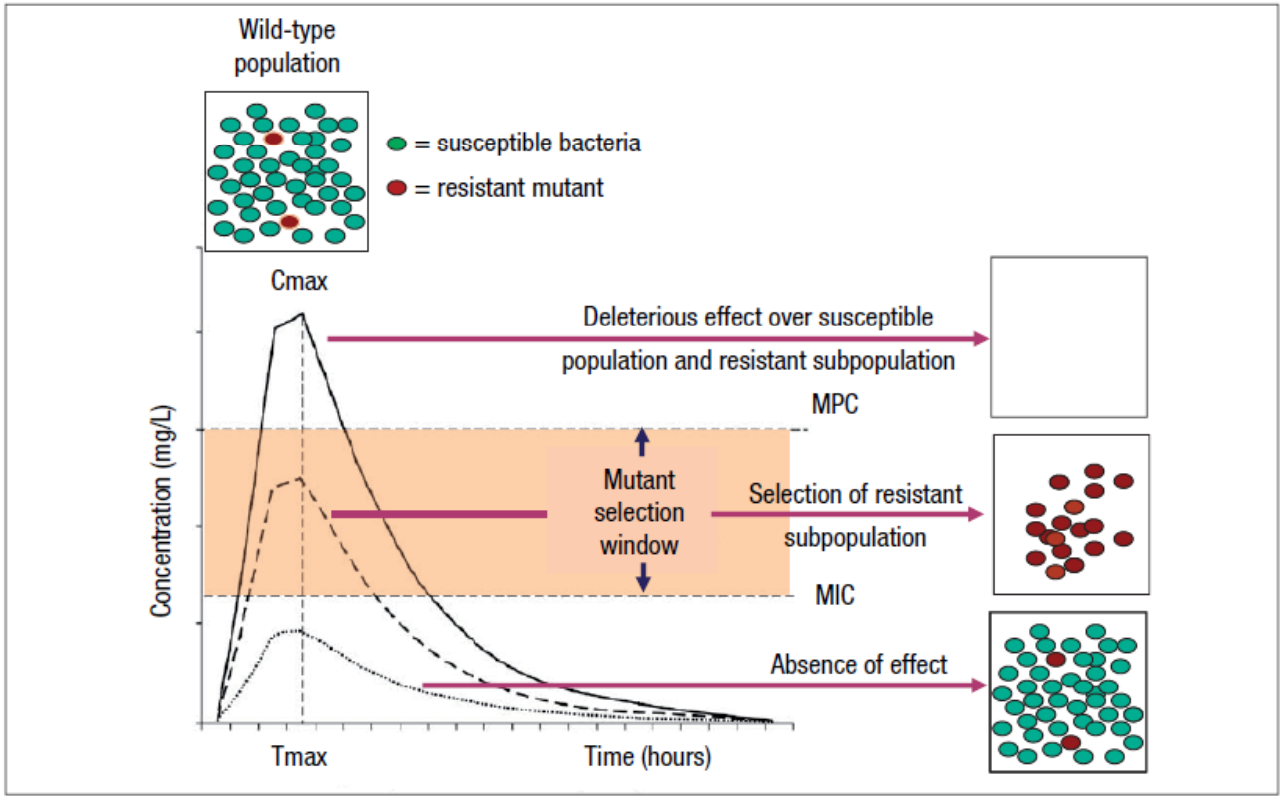
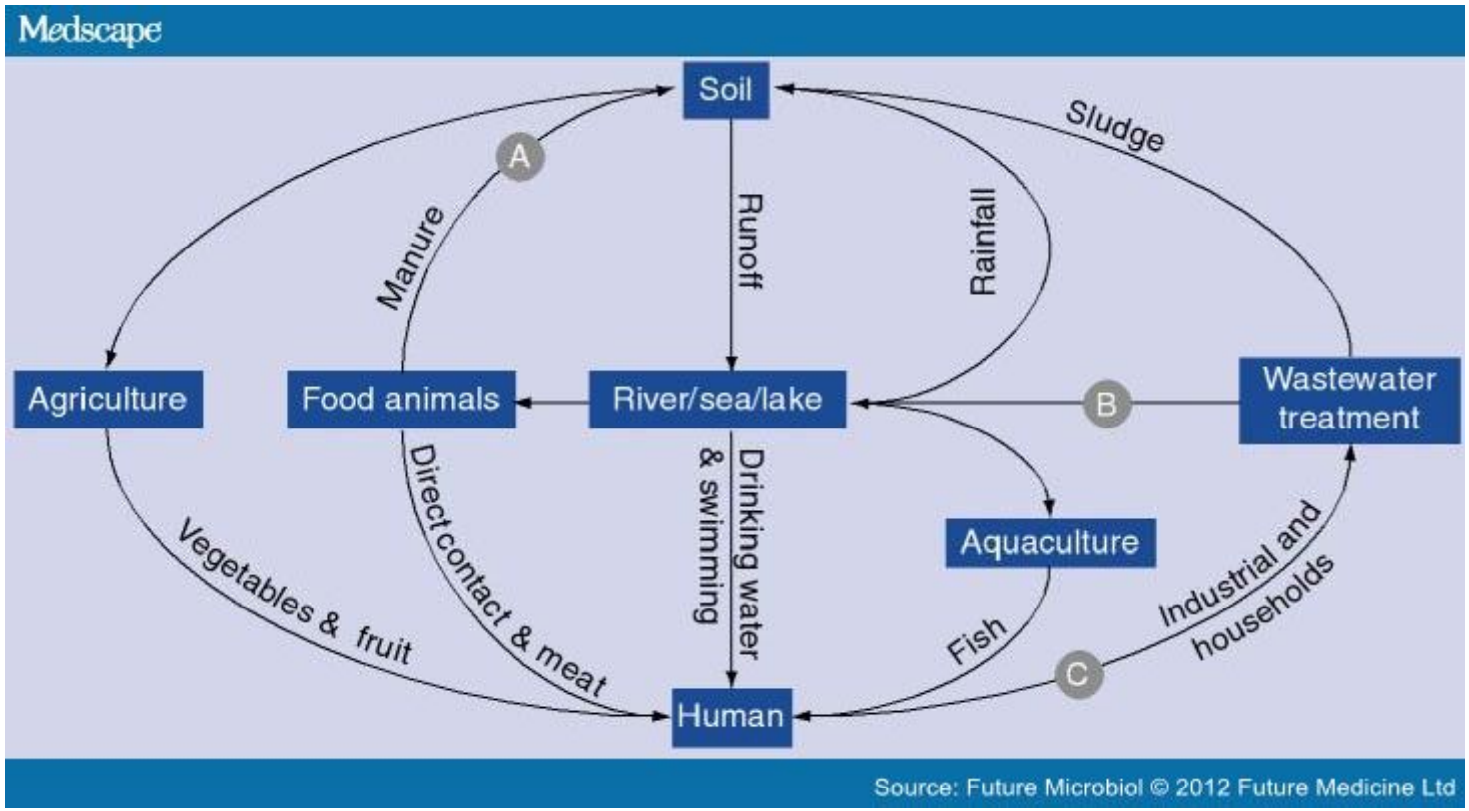


Figure 1. Mutant selection window (MSW) and mutant prevention concentration (MPC). Square boxes represent the bacterial population and curves the pharmacokinetics (concentration over time) of an antimicrobial agent. MSW is the concentration range in which resistant mutants can be selected and is delimited by the minimal inhibitory concentration (MIC) and the MPC. Above MPC, the selection of resistant mutant subpopulation should not be possible and the susceptible population is abolished, whereas below MIC values no effect over susceptible and resistant subpopulations is theoretically produced.

Transmisión horizontal y diseminación clonal de R: Reservorios

- Flora intestinal del hombre y otros animales
- Areas de alta exposición AB con elevada contaminación microbiana: hospitales (UCIP, UCIN), granjas, plantas depuradoras.
- Suelo, subsuelo y aguas subterráneas y de superficie

Interacción entre reservorios y expansión de la AB-R

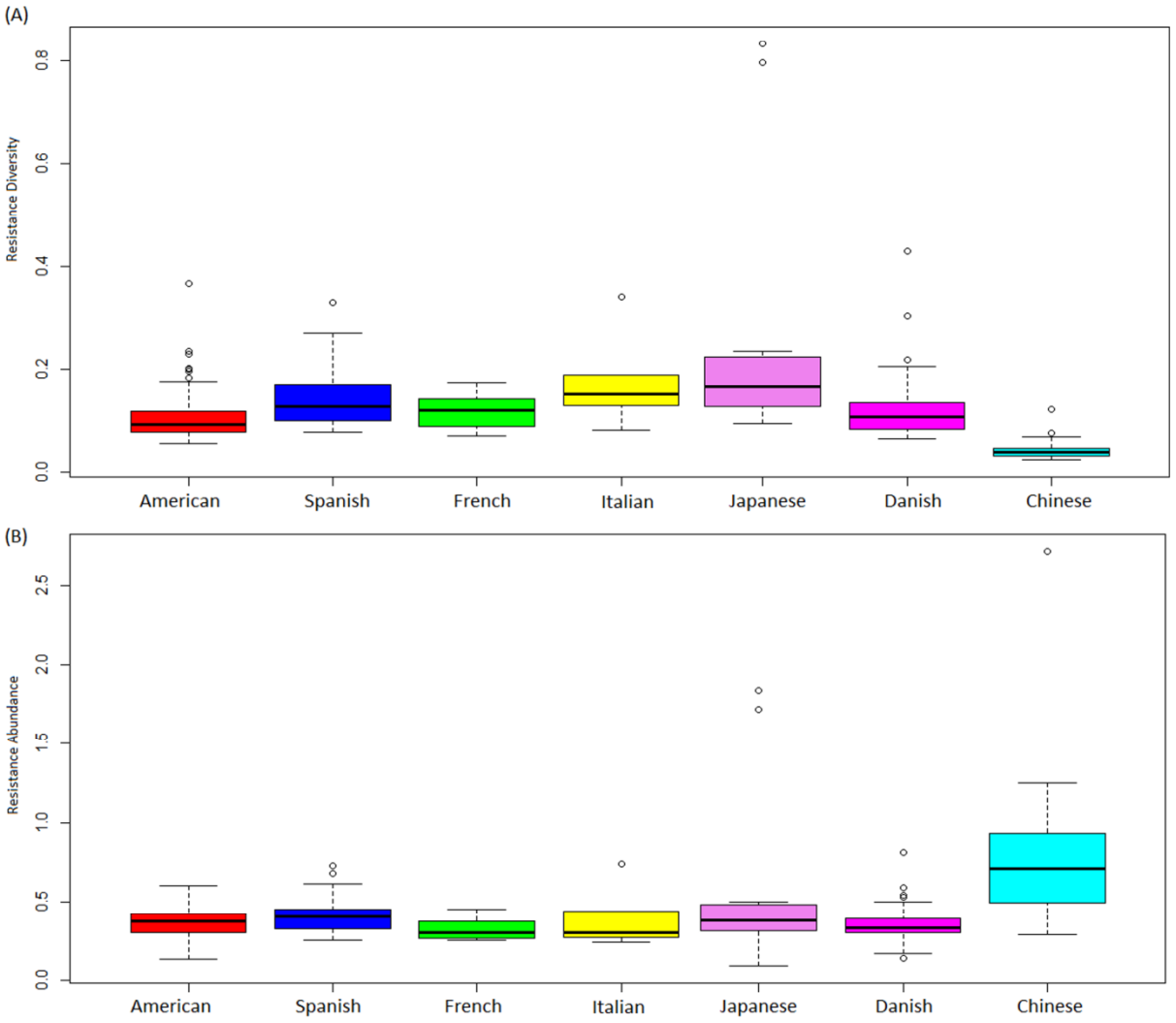


Microbioma humano

- Microorganismos colonizantes (boca, narinas, intestino, piel)
- Nºbacterias 10 veces > nº de celulas cuerpo humano
- > en intestino: 800-1000 spp distintas (80% nunca cultivadas)
- Papel crucial en la vida humana
- Variabilidad microbioma entre individuos, dependiente de: dieta, geografía, fisiología, enfermedades, fc. intestino
- AB modifican, a veces permanentemente, el microbioma int.
- Estudios de DNA metagenómico y genómico: Presencia de pool de genes de R en microbioma intest. en individuos sanos.

Sommer MOA. Functional characterization of the antibiotic resistance reservoir in the human microflora. Science 325, 1128–1131 (2009).

Microbioma intestinal: Genes de AB-R



A) Diversidad de genes de AB-R en individuos de diferentes nacionalidades

B) Cantidad de genes de AB-R en individuos de diferentes nacionalidades

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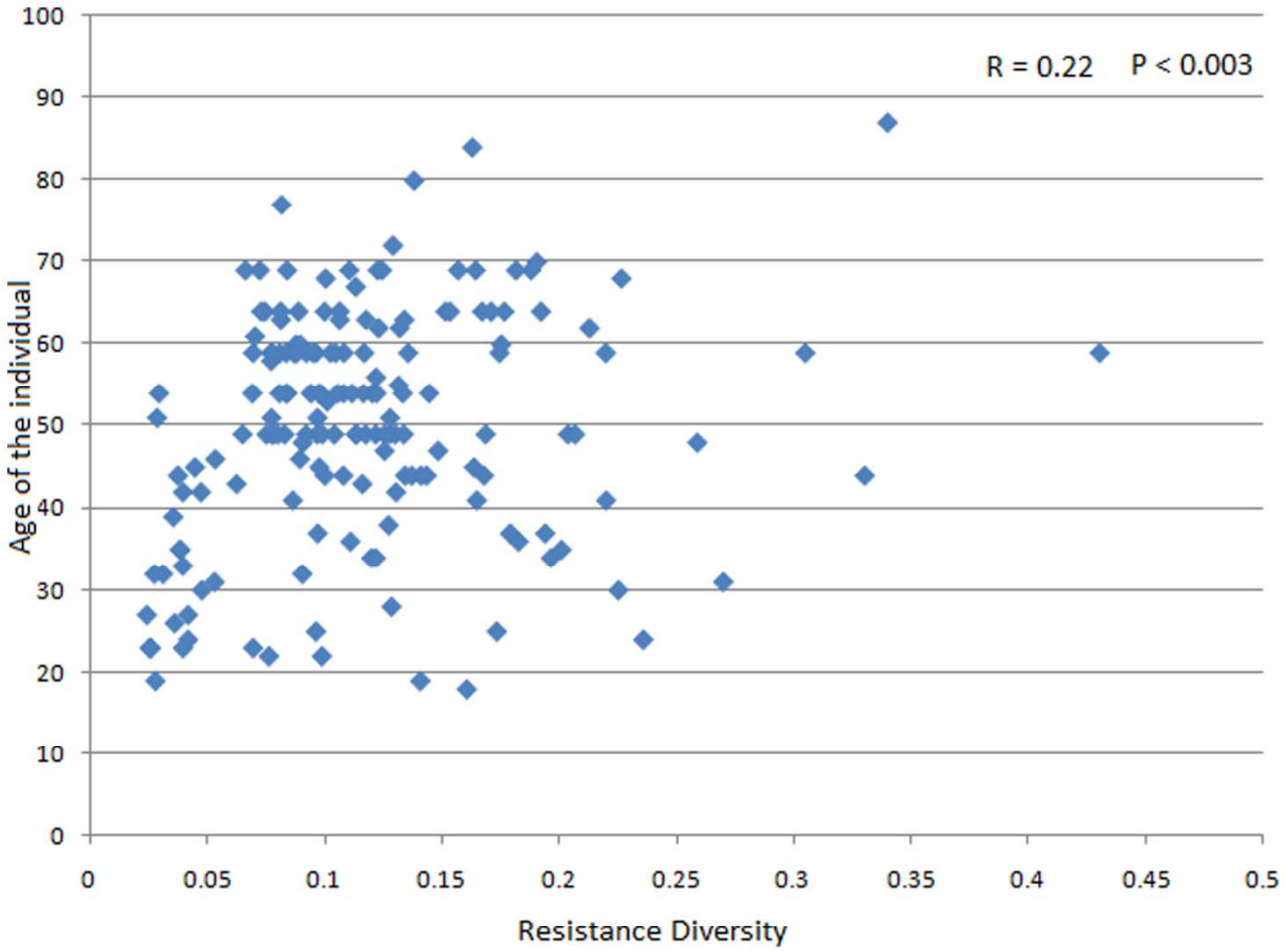
Genes de AB-R en la microflora intestinal



Evolución de la diversidad de genes de AB-R, según la edad en 267 individuos

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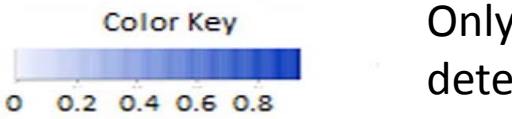
Genes de AB-R en la microflora intestinal



Only those antibiotics for which the resistance genes have been detected in at least 10% of the gut metagenomes are shown

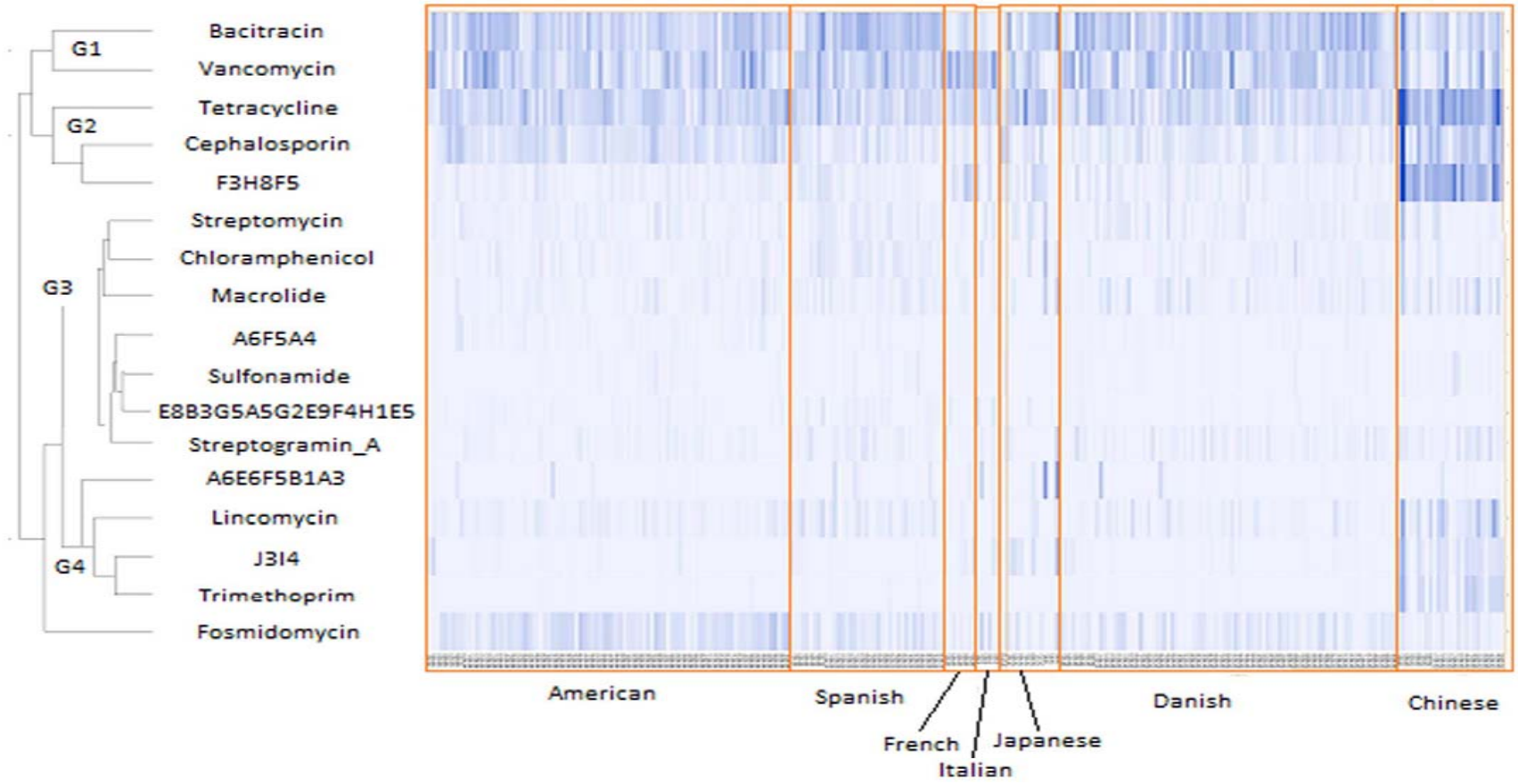


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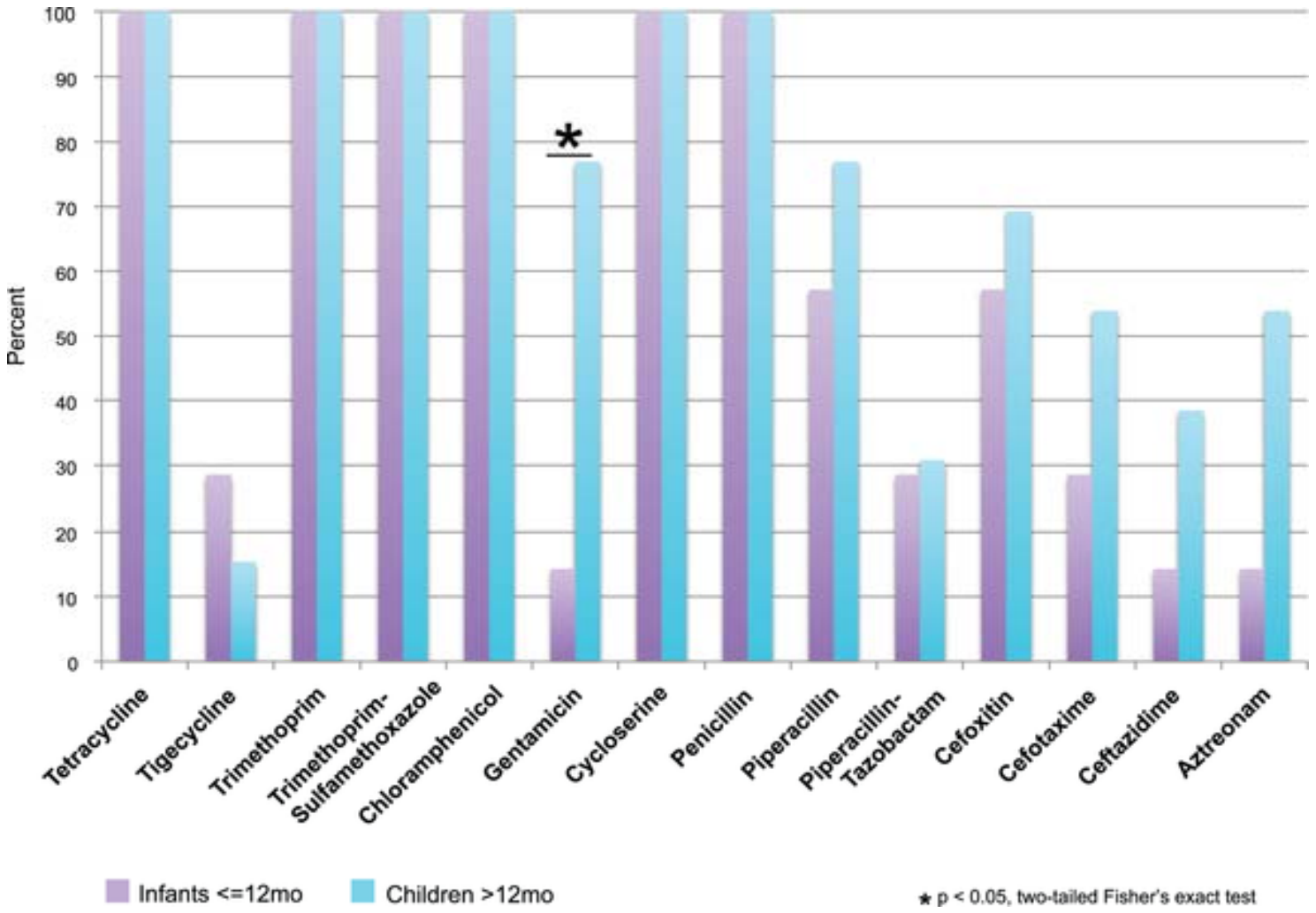
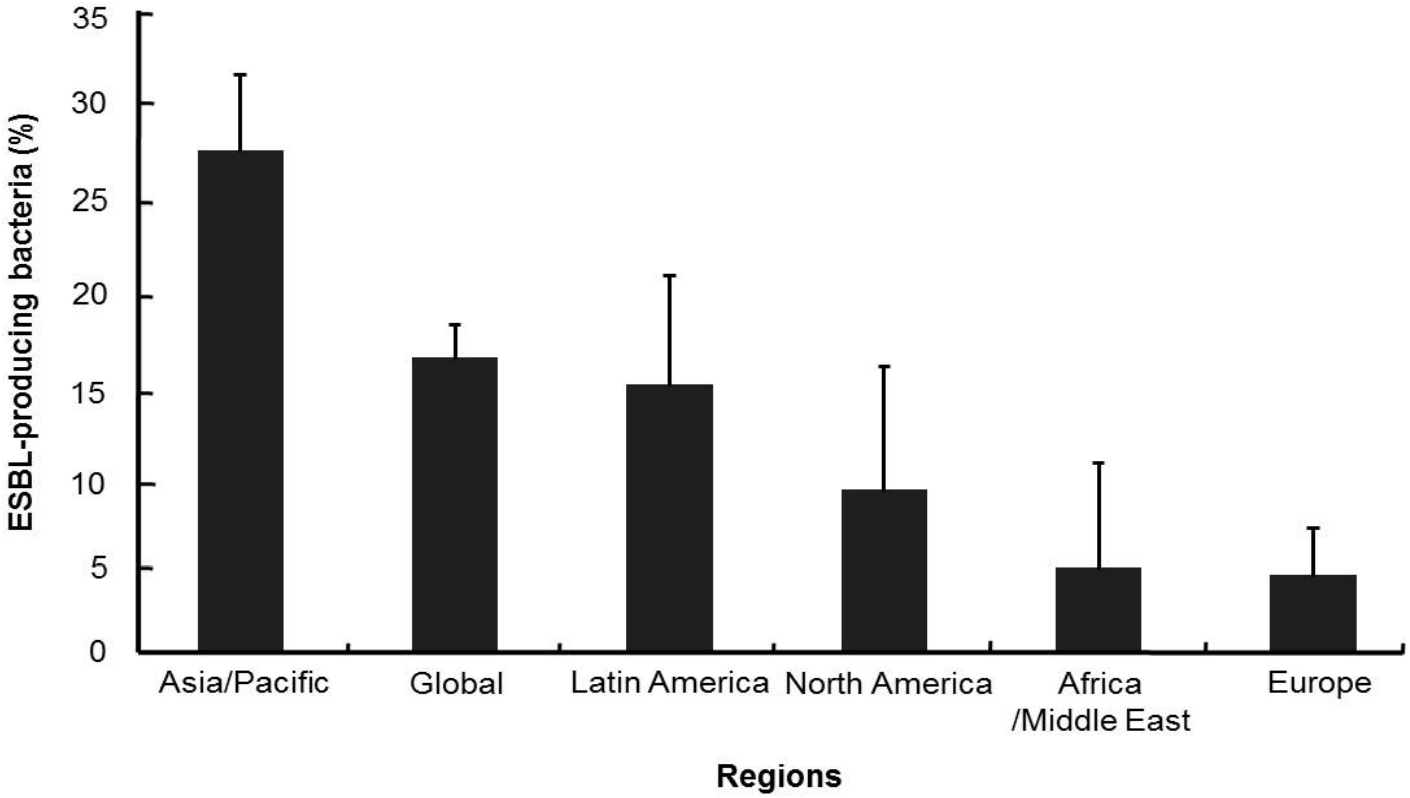
Figure 1. Antibiotic selections for which resistance was observed.



Moore AM, Patel S, Forsberg KJ, Wang B, et al. (2013) Pediatric Fecal Microbiota Harbor Diverse and Novel Antibiotic Resistance Genes. PLoS ONE 8(11): e78822. doi:10.1371/journal.pone.0078822
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0078822

Diferencias geográficas en patrones de patógenos R



Aislamientos de enterobacterias BLEE en pts. con apendicitis (2008-2010)

Interacción entre HOSPITAL y otros reservorios

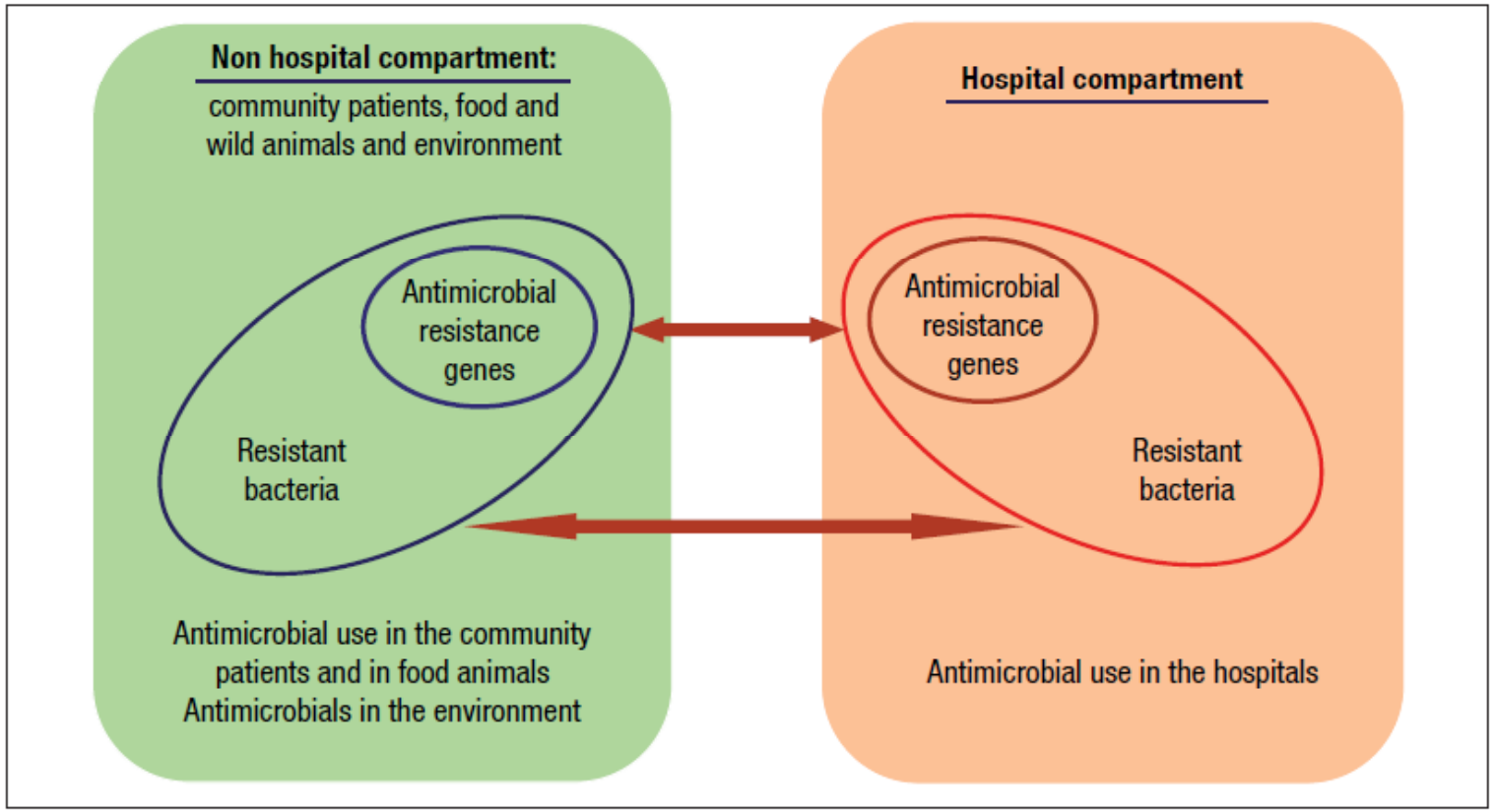
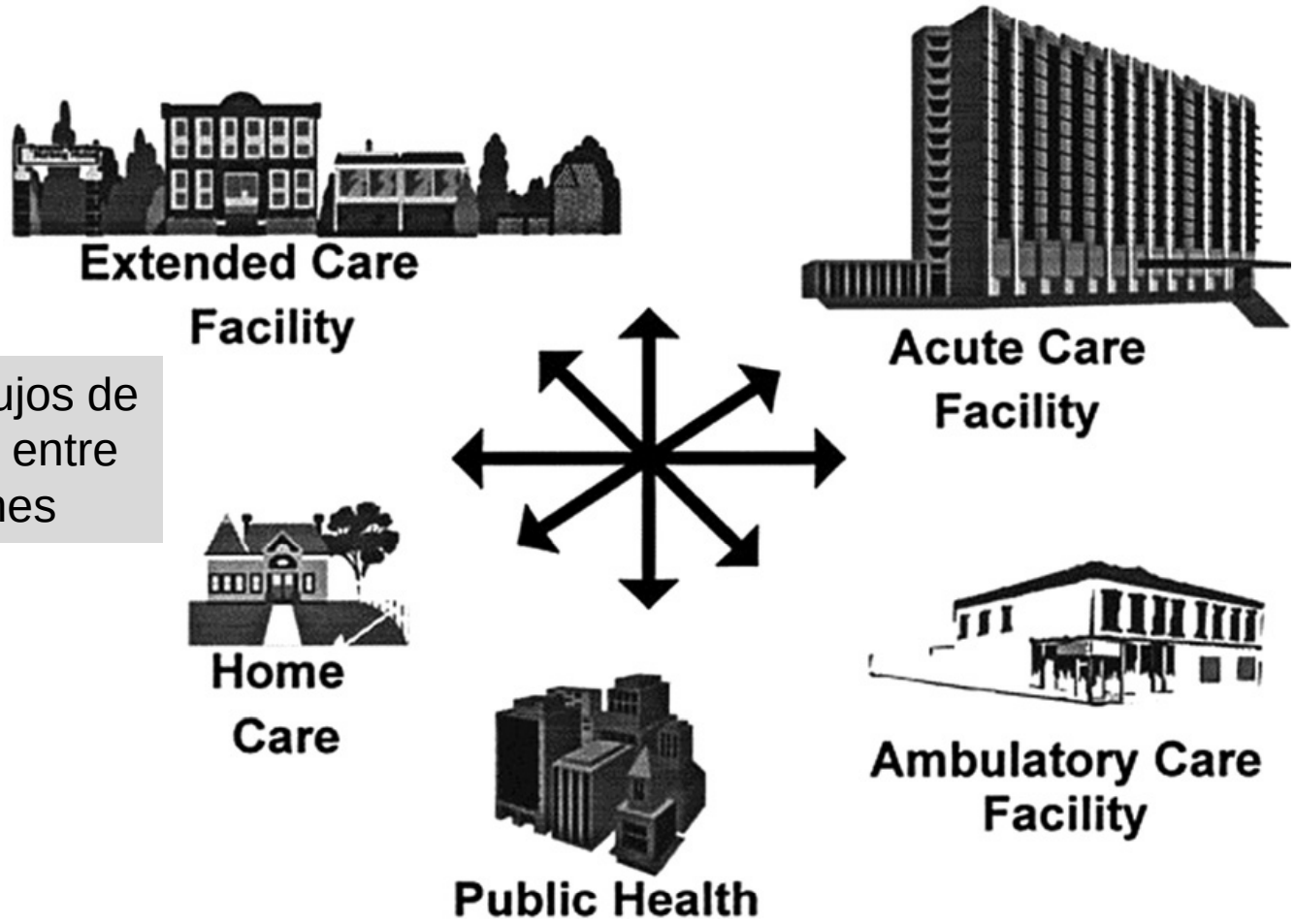


Figure 2. Compartments of selection of resistant bacteria. Currently, various compartments are interconnected and antibiotic policy programs should be globally implemented.

Compartimento hospitalario: interacciones

Figura 1. Extensión de la asistencia sanitaria a otros ámbitos no hospitalarios.
Adaptado de Jarvis W, Waller L. Centers for Disease Control and Prevention, 1998.



Existen flujos de pacientes entre instituciones

Compartimento hospitalario foco de generación y transmisión de R: Causas

A) **Infecciones cruzadas** (origen del 40% IN): políticas inadecuadas de control infección (escasa higiene, inadecuada desinfección, hacinamiento...)

B) **Sobreuso i uso inadecuado de AB:**
- Variabilidad de médicos prescriptores: especialidad, formación, motivación, accesibilidad consultores infecciosas....
- Variabilidad errores de prescripción:
bajo umbral indicación, retraso inicio, escaso conocimiento patrones de R locales, errores elección farmaco/dosis/via, falta de simplificación trat. empírico

C) **Interacción con otros compartimentos clínicos y no-clínicos**

- *Enferm Infecc Microbiol Clin. 2013;**31(Supl 4):12-15***

Era post-AB:
Microorganismos MDR= Situación de extrema gravedad

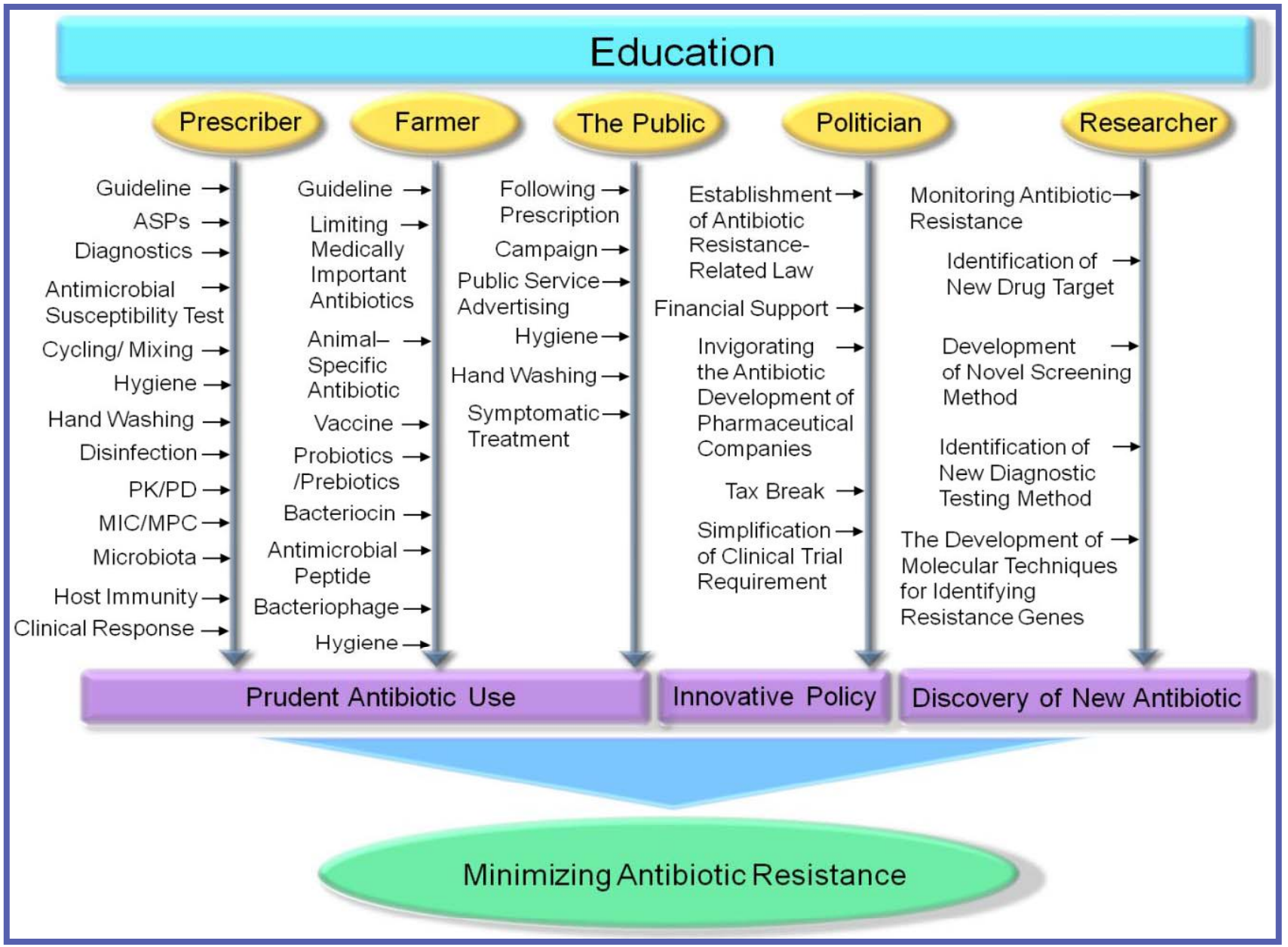
Incremento progresivo de pacientes con infecciones graves que no podemos tratar de forma eficaz por falta de AB adecuados.

- Estancias prolongadas
- Costes elevados
- Fracaso terapéutico
- Mortalidad relacionada

Respuesta integral y coordinada

1. Incentivar investigación y desarrollo de nuevos AB
2. Desarrollar nuevas técnicas de diagnóstico rápido
3. Politicas globales que regulen el uso no-clínico de AB
4. Programas de optimización del uso de AB: PROA
5. Programas de control epidemiológico de la infección: limpieza, desinfección, higiene, evitar hacinamiento...

5. Políticas de información y educación



Chang-Ro Lee Int. J. Environ. Res. Public Health 2013, 10: 4274-4305