

Marc Dumont

*The evolution of antibiotics and resistance
against them*



Food Standards Agency
November 25, 2016



*Introduction to the enemy: microbes
Or, are they our friends?*

Astronomical numbers of microbes on the planet:

- ✧ Estimated number of stars in the universe: 1×10^{22}
 - ✧ Estimated number of grains of sand on the planet: 7.5×10^{18}
 - ✧ Estimated number of bacteria on the planet: 5×10^{30}
 - ✧ If all bacteria were lined up end-to-end, they'd stretch 1 billion light years
- Microorganisms (Prokaryotes)*
- ✧ As much carbon in bacteria as plants. *Dry* weight of bacterial cells between $350\text{--}550 \times 10^9$ tonnes
 - ✧ About equal number of bacterial and human cells in our bodies
 - ✧ Human adult excrete their own weight in faecal bacteria each year
 - ✧ Number of genes contained within this gut flora outnumber that contained within our own genome 150-fold
 - ✧ 1 g of dental plaque contains 1×10^{11} bacteria (roughly the same number of humans that have ever lived)
 - ✧ A teaspoon of soil has about 1×10^9 bacteria

Scaling laws predict global microbial diversity

Kenneth J. Locey^{a,1} and Jay T. Lennon^{a,1}

| PNAS | May 24, 2016 | vol. 113 | no. 21

Earth is home to an estimated trillion microbial species
99.999% remain undiscovered



*Killing your neighbour alleviates
competition for resources*



Killing your neighbour alleviates competition for resources

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Soils are largest source of microbial diversity



fera.co.uk

Highly limited resources and space leads to extreme competition played out over billions of years of evolution

Misconception 1

AMR is “unnatural”

Many microbes in pristine environments are resistant to antibiotics
✧ Referred to as the “resistome”

Sampling the Antibiotic Resistome

Vanessa M. D’Costa,¹ Katherine M. McGrann,¹ Donald W. Hughes,² Gerard D. Wright^{1*}

The Soil Microbiota Harbors a Diversity of Carbapenem-Hydrolyzing β -Lactamases of Potential Clinical Relevance

Dereje Dadi Gudeta,^a Valeria Bortolaia,^a Greg Amos,^b Elizabeth M. H. Wellington,^b Kristian K. Brandt,^c Laurent Poirel,^d Jesper Boye Nielsen,^e Henrik Westh,^{e,f} Luca Guardabassi^a

The Shared Antibiotic Resistome of Soil Bacteria and Human Pathogens

Kevin J. Forsberg,^{1*} Alejandro Reyes,^{1*} Bin Wang,^{1,2} Elizabeth M. Selleck,³ Morten O. A. Sommer,^{4,5†} Gautam Dantas^{1,2†}

Antibiotic Resistance Is Prevalent in an Isolated Cave Microbiome

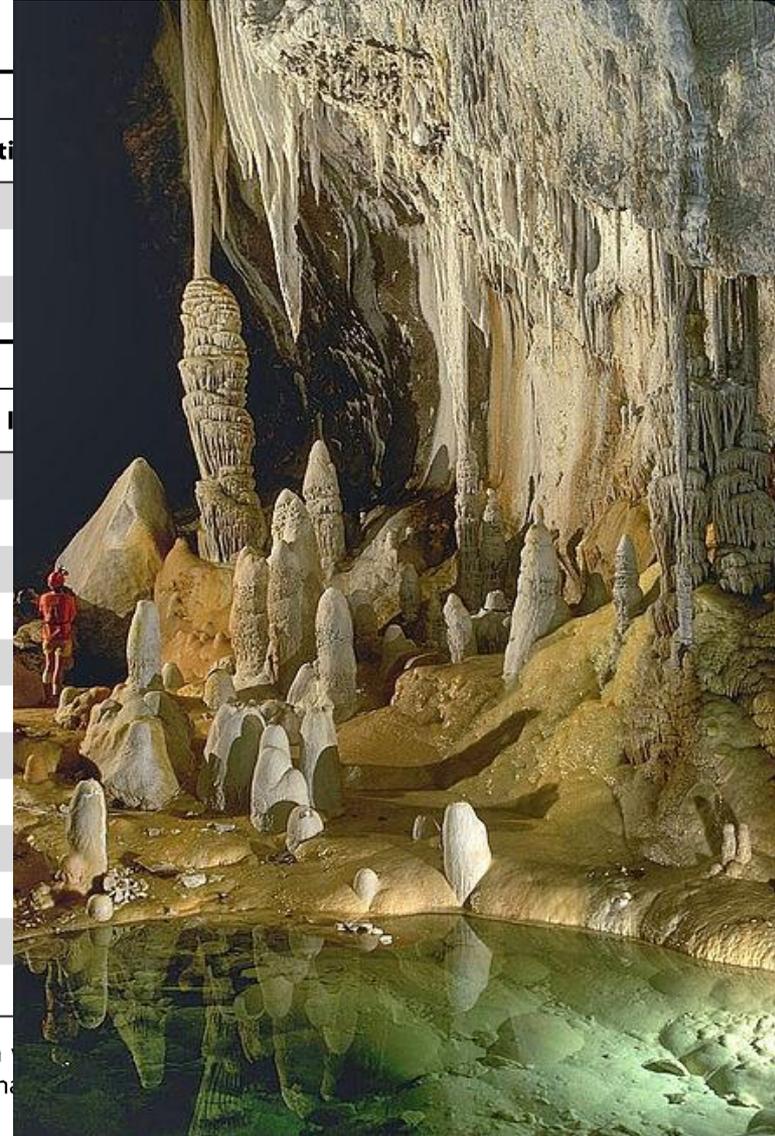
Kirandeep Bhullar¹, Nicholas Waglechner¹, Andrew Pawlowski¹, Kalinka Koteva¹, Eric D. Banks², Michael D. Johnston², Hazel A. Barton², Gerard D. Wright^{1*}

Gram-positive isolates

Antibiotic	Resistant Strains	Number of antibiotic Inacti
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Lechuguilla cave, New Mexico

0

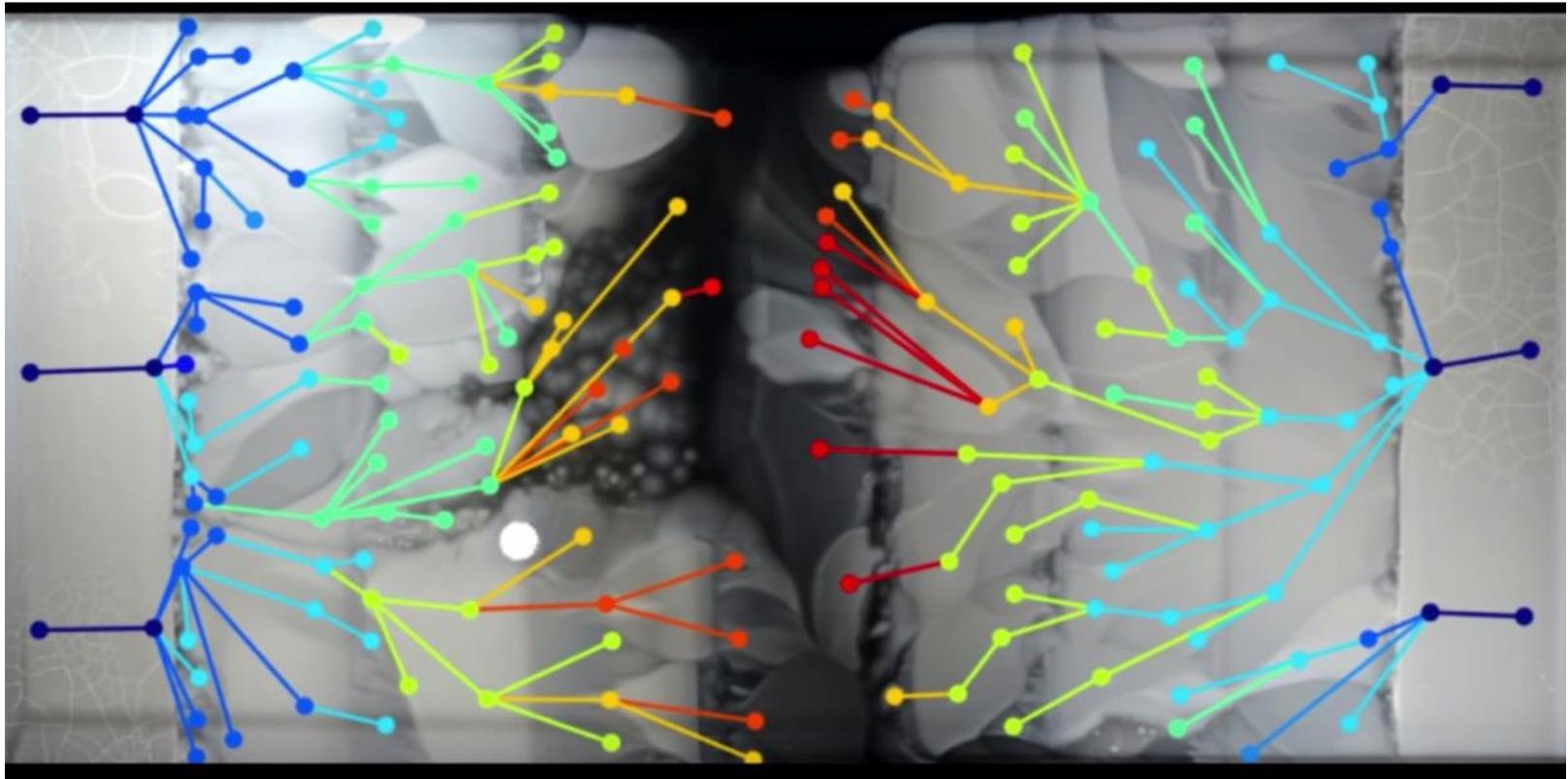


Spatiotemporal microbial evolution on antibiotic landscapes

Science

Michael Baym,¹ Tami D. Lieberman,^{1*} Eric D. Kelsic,¹ Remy Chait,^{1†} Rotem Gross,²
Idan Yelin,² Roy Kishony^{1,2,3‡}

E. coli evolution of trimethoprim resistance on a large Petri dish



(Concentrations: 0, 3, 30, 300 and 3000 $\mu\text{g}/\text{ml}$)

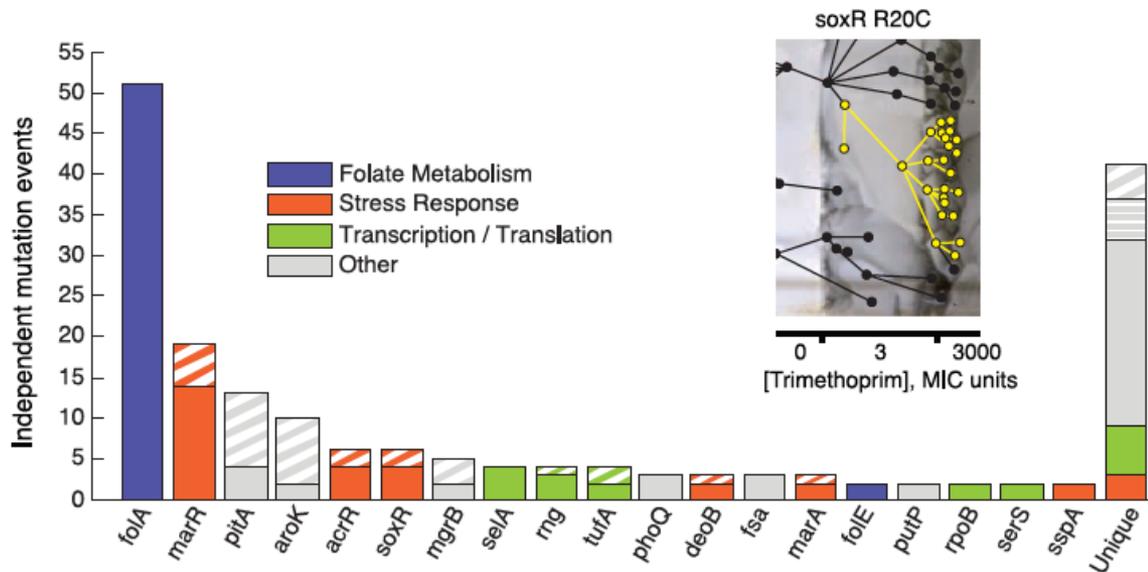
Spatiotemporal microbial evolution on antibiotic landscapes

Michael Baym,¹ Tami D. Lieberman,^{1*} Eric D. Kelsic,¹ Remy Chait,^{1†} Rotem Gross,² Idan Yelin,² Roy Kishony^{1,2,3‡}

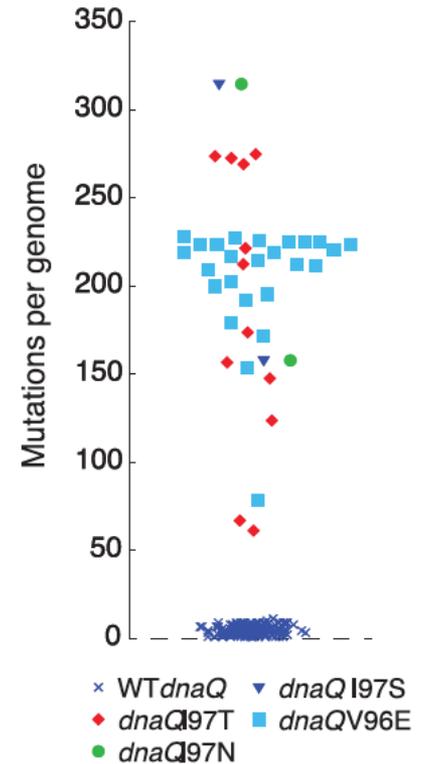
Questions: How long did it take *E. coli* to evolve resistance to 3000 $\mu\text{g/ml}$ trimethoprim?

How many mutations did the resistant *E. coli* strains accumulate?

What were the mutations?



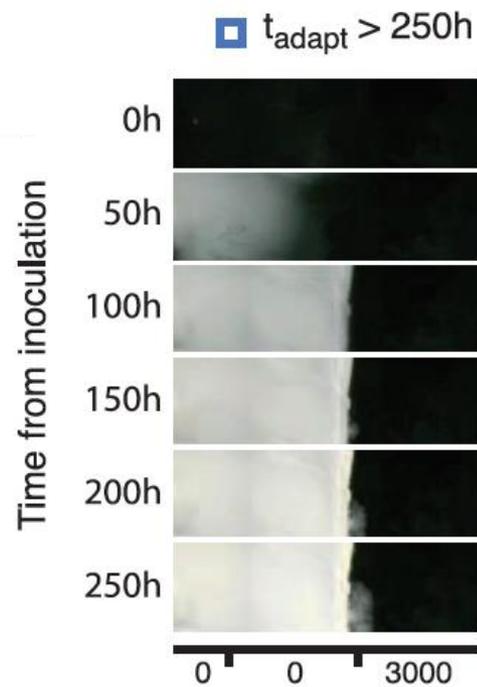
11 days



Spatiotemporal microbial evolution on antibiotic landscapes

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Idan Yelin,² Roy Kishony^{1,2,3‡}

“Initial adaptation to low drug concentrations facilitates later adaptation to high concentrations”



Misconception 2

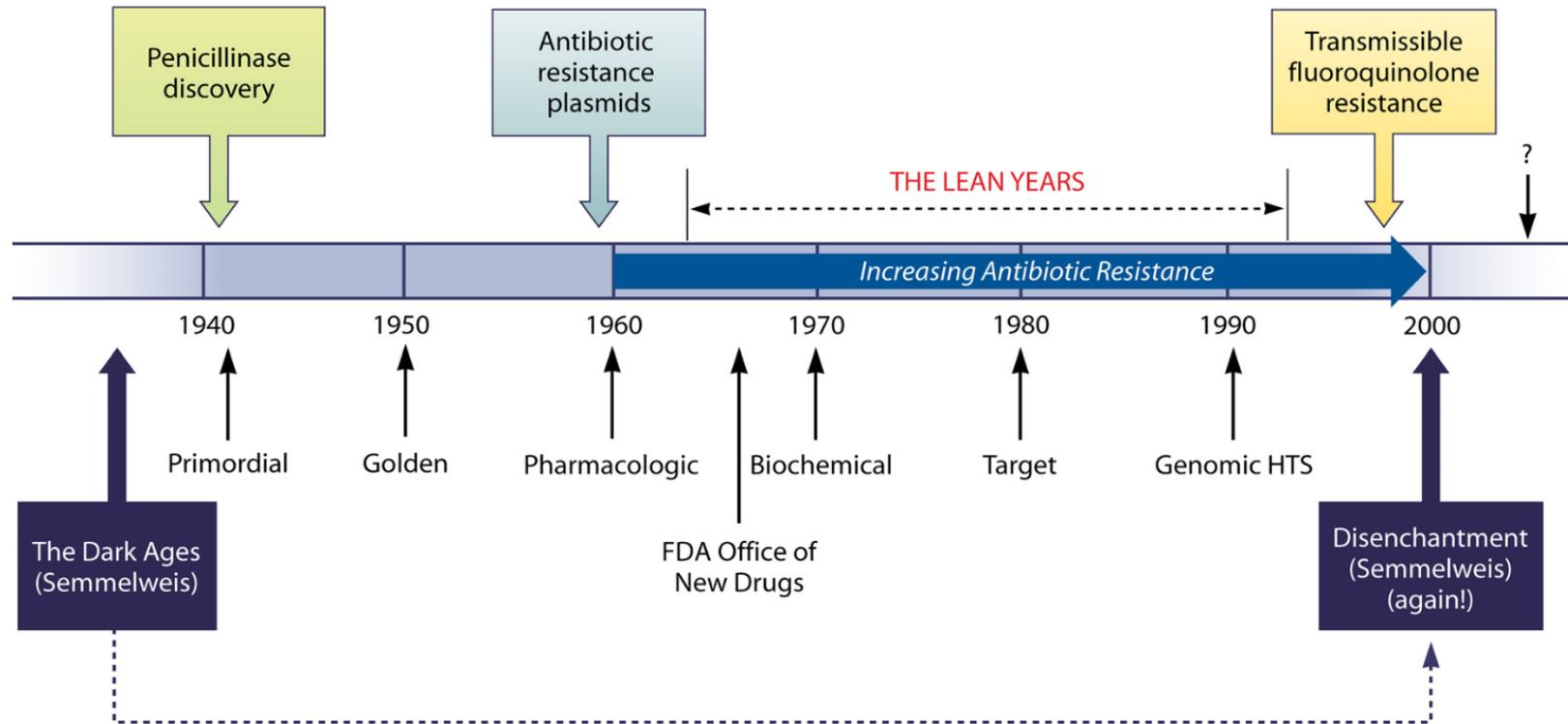
*Microbes are less evolved than
multicellular organisms*

Origins and Evolution of Antibiotic Resistance

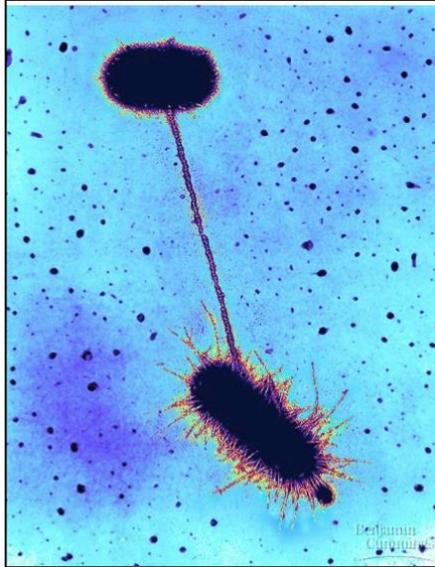
Julian Davies* and Dorothy Davies

*Department of Microbiology and Immunology, Life Sciences Institute, University of British Columbia,
2350 Health Sciences Mall, Vancouver, British Columbia V6T 1Z3, Canada*

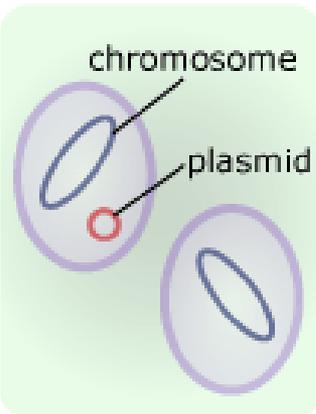
Events in the Age of Antibiotics



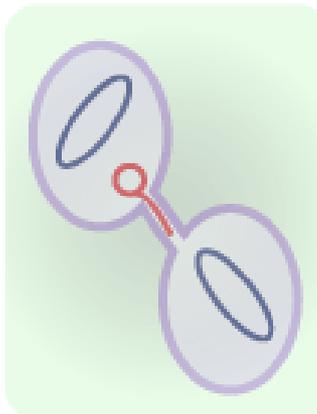
Plasmids and Bacterial Conjugation



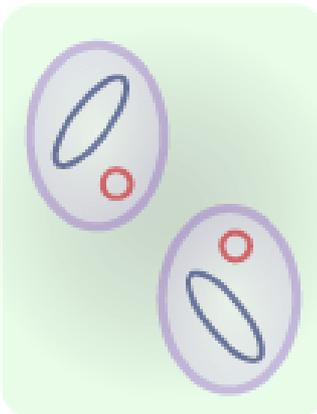
1. One bacterium contains a plasmid to be transferred.



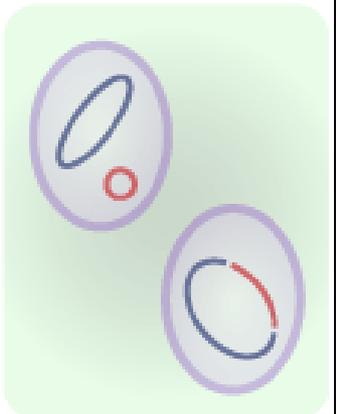
2. A connection forms and the plasmid is copied.



3. Both bacteria now contain the plasmid.



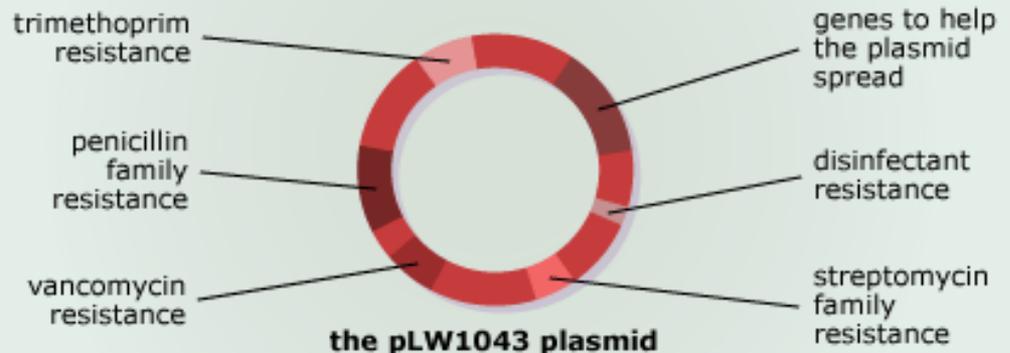
4. The recipient may even integrate the plasmid into its chromosome.



Genetic Analysis of a High-Level Vancomycin-Resistant Isolate of *Staphylococcus aureus*

Linda M. Weigel,^{1*} Don B. Clewell,² Steven R. Gill,³ Nancye C. Clark,¹ Linda K. McDougal,¹ Susan E. Flannagan,² James F. Kolonay,³ Jyoti Shetty,⁴ George E. Killgore,¹ Fred C. Tenover¹

A single plasmid can carry the genes to resist many different antibiotics.



Summary

1. Bacterial pathogens can be a highly adaptive enemy
2. AMR can evolve in days
3. AMR genes can be transferred within minutes on plasmids
4. Soil is an enormous reservoir of diversity – including “natural” AMR
5. We are introducing potential pathogens, plasmids and antibiotics into soil; what are the risks?
 - ✧ How long do pathogens or their genes survive in soil?
 - ✧ Are antibiotics selecting for more resistance within soils?
 - ✧ Are we risking creating new pathogens?
 - ✧ Do AMR genes transfer between exogenous and native microbes?
 - ✧ What are the risks to crops, livestock, farmers and consumers?

Acknowledgments

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