Monitoring microbiological quality and safety through diagnostics

The MIDASS experience

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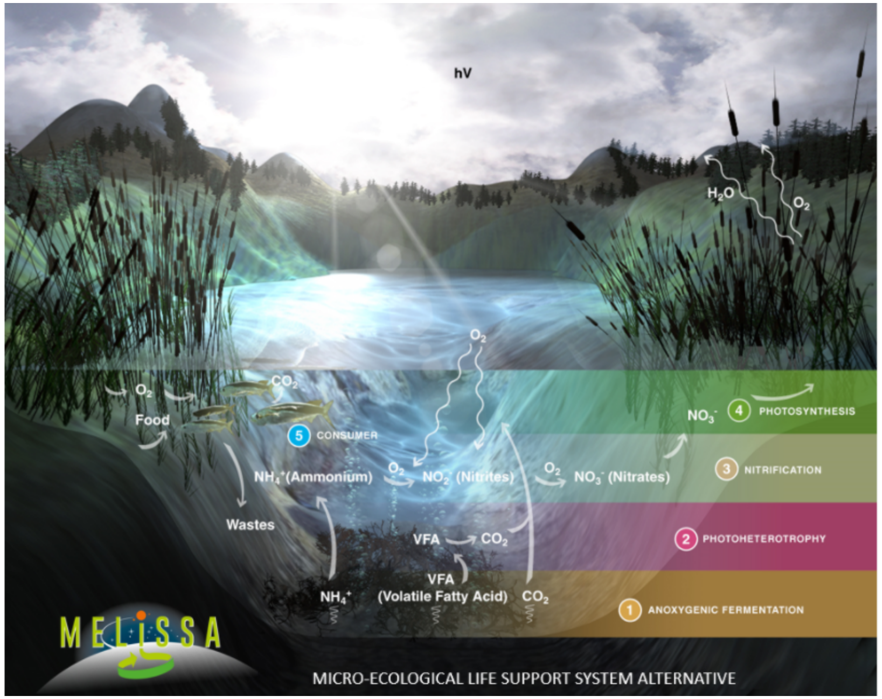
November 5

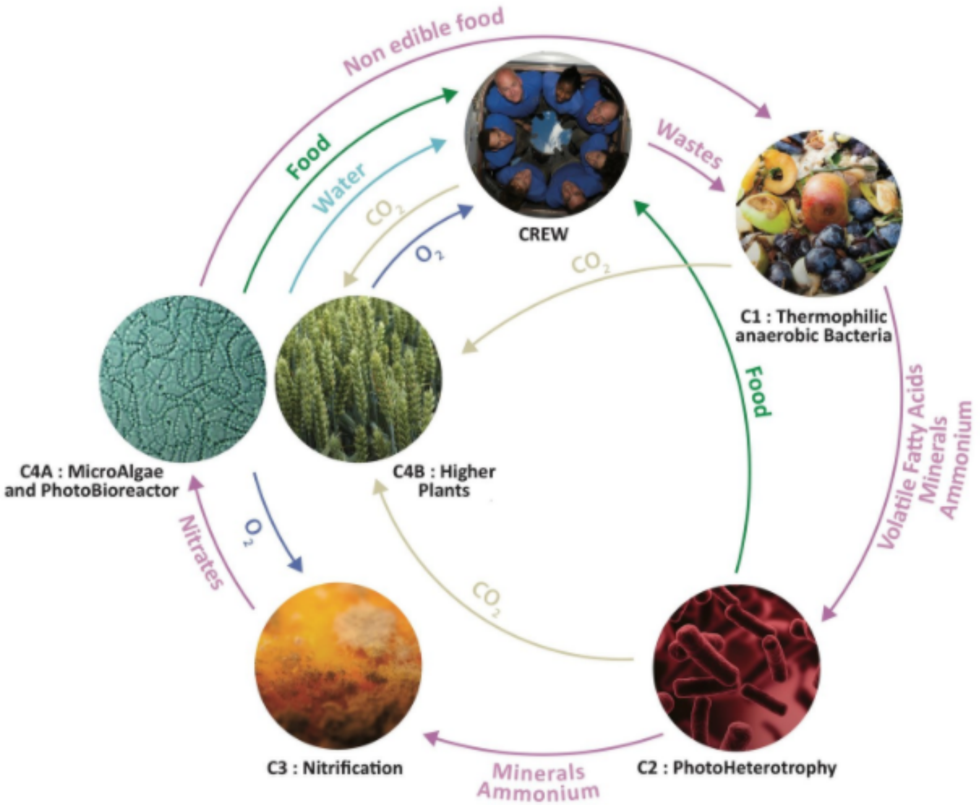
PIONEERING DIAGNOSTICS

REGENERATIVE LIFE SUPPORT SYSTEM TO SUPPORT LONG-TERM SPACE MISSIONS IS AN AMBITIOUS GOAL



- **MELiSSA aims at**
  - the use of wastes & light as a source of energy.
    - i.e. organic wastes and CO2,
  - to support the production of food,
  - to recover water
  - to regenerate the atmosphere,

THE MELISSA PILOT: MASTERING MICROBIOLOGY (amongst other things…)



- Microbiological quality is a must
- Microbiological safety is a must

KNOWLEDGE TOOLS
ARE ESSENTIAL:
= monitoring / diagnostics
Physical, chemical, microbiological

ENCOUNTER OF THE 3RD TYPE: WHEN ESA MEETS THE TERRESTRIAL INDUSTRY

Leveraging terrestrial know-how

LEVERAGING TERRESTRIAL KNOW-HOW

- **Partner with a *in vitro* diagnostics (IVD) company**
- **Medical IVD (infectious diseases, metabolic disorder) : detect / measure / monitor the presence of disease-causing agents or substances from a body sample analysed *in-vitro***
- **Industry IVD: *idem* from food, drug or air samples to assess the quality & safety of the production process and final product**

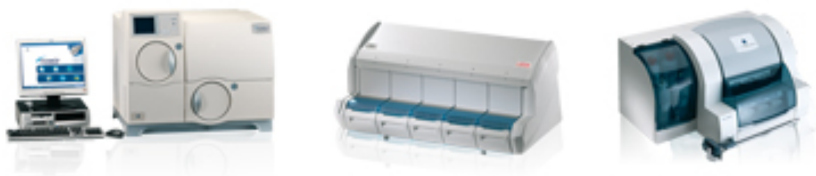
DIAGNOSTIC SYSTEMS

EXAMPLES OF SAMPLES


Blood


Urine


Food matrix



System Approach:

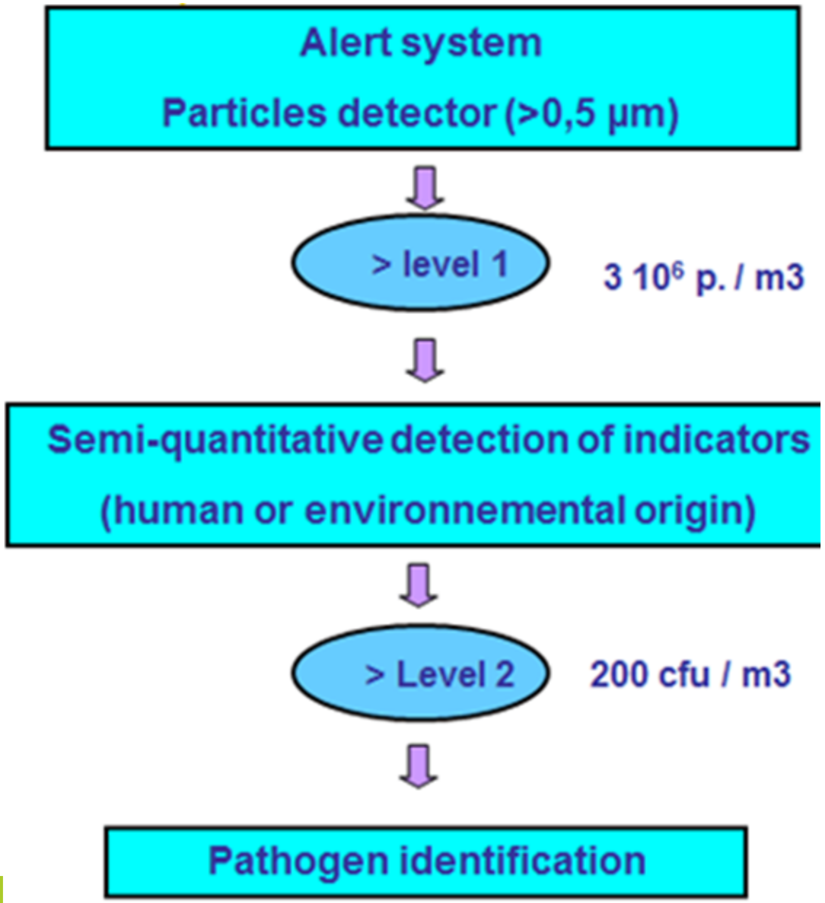

REAGENTS


INSTRUMENTS


SOFTWARE


SERVICES

The MIDASS project:
Microbial detection in air system for space



Objective:

develop a rapid, miniaturised, automated system for sampling and monitoring the microbiological quality of air and surfaces.

Based on molecular biology

- **ESA applications (in-flight prototype)**
  - Long-term: long-duration space flight: crew safety and hardware integrity
- **bioMérieux applications (terrestrial prototype:**
  - Rapid air and surface monitoring to ensure safety of sterile pharmaceutical products *eg* vaccines

Shared benefits:

- **bioMérieux's expertise in IVD systems development and manufacturing**
- **ESA's drive for a technological breakthrough**
- **Whereas sharing technological and financial risks**

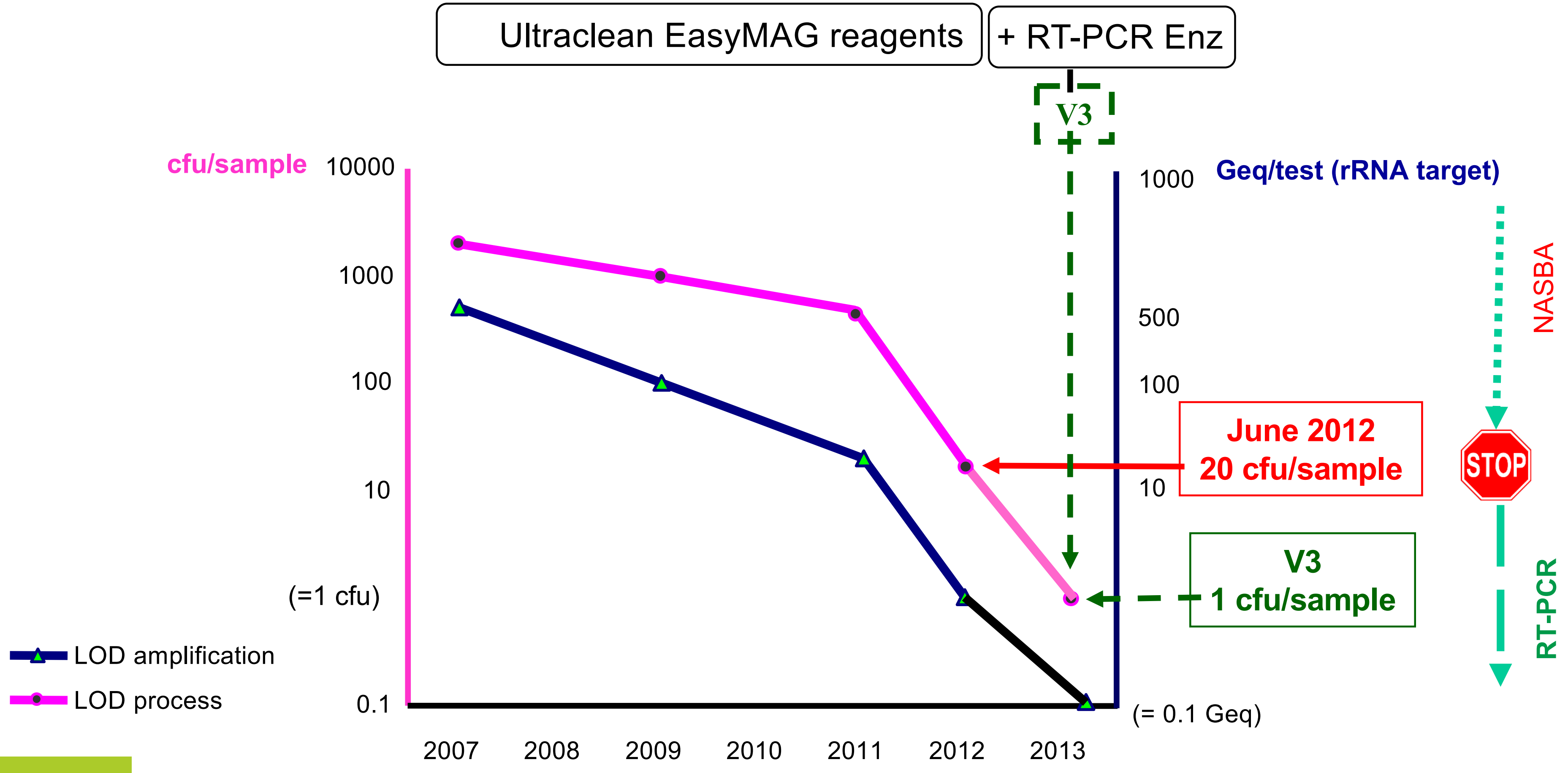
Started 2001

MIDASS requirements / challenges

- **Design a complete solution fitting customer's needs (ESA and Sterile Pharmaceutical production)**
- **Design a routine workflow of a complex protocol (ca. 100 steps)**
- **Achieve routine performances for an innovative test (all bacteria/all fungi):**
  - Sensitivity: 1 cfu/sample (1 M^3)
  - Quantification: 3-log dynamic range
  - No false-positives: ultra-clean reagents (free of nucleic acids)
- **Obtain recognition for a non-culture based interpretation tool**
- **Reach profitable cost of goods for reagents**

Terrestrial demonstrator delivered in 2014

MIDASS microbiological achievement



MIDASS for space: successful PDR in 2014

Core of MIDASS system

Solution retained:
Materialized prototype

Functions:

1. Air impaction (future apps: surfaces, water)
2. Bacteria, yeasts and mould lysis
3. Nasba amplification of target-specific RNA
4. Real time fluorescence detection

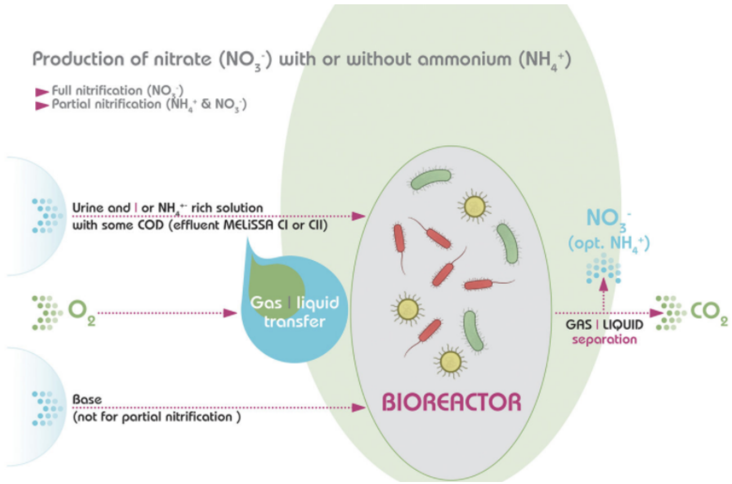
Leverage MIDASS for MELiSSA

MELISSA MICROBIOLOGICAL CONTROL REQUIREMENTS

- **Genetic stability of strains and plants (Ground and Space environment) during long-term mission**

- **• Axenicity of the microbial processes:**
  - – CII: Rhodospirillum rubrum S1H ATCC25903
  - – CIII Nitrobacter winogradskyi / Nitrosomonas europea
  - – CIVa: Arthrospira sp. PCC8005

- **• Microbial control of the environment**
  - Life Support System should not contaminate the crew and the environment



TRANSLATION IN THE MPP FACILITY

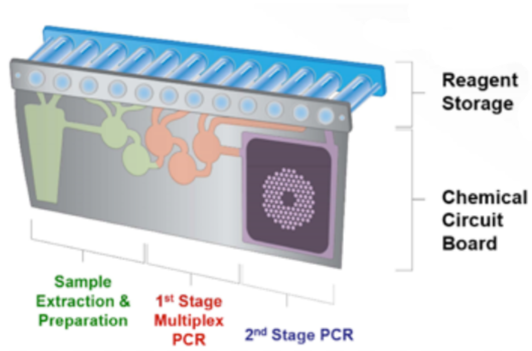
Define an ideal scenario of environmental monitoring within the MPP facilities: a sampling plan (critical points frequency…etc) including

- **Environmental monitoring of Air & Surface in MPP facilities : MiDASS**
  - surface of compartments, mainly CII and CIII
  - Check ISO 7 spec is OK : detect < 1h30 more of less than 100 cfu / 25 cm2, quantitative monitoring
  - Extend to testing air confined around Melissa compartments
- **Compartments (including reactors) & their interfaces**
  - purity of ferments, no contamination, no genetic drifts
- **MPP Utilities**
- **Consumables (Medium…etc)**

THEN OUR COMMON PATH DIVERGED…

- **bioMerieux**
  - The industry division in charge of the terrestrial changed its priorities
  - But at the same time the medical division leverage the MELISSA know-how to buy a US company having matured a similar concept for medical applications

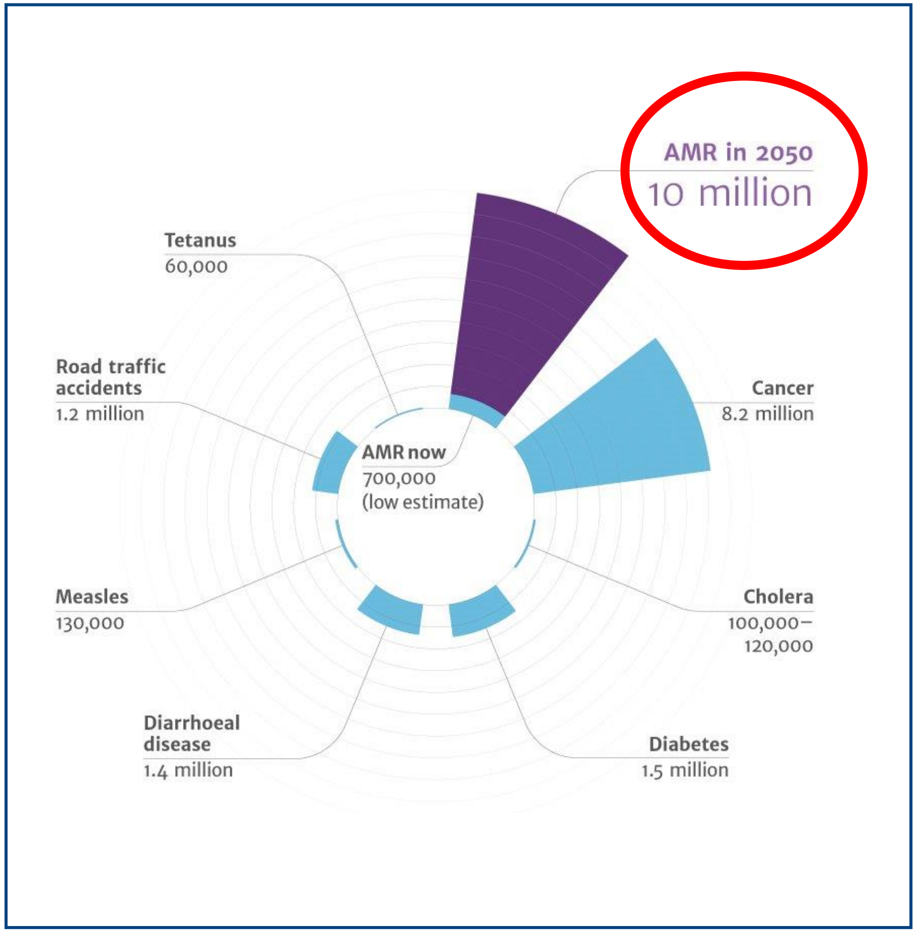
- **ESA**
  - After PDR (TRL 5), the project was transferred to another division where perception of the microbiological risk was low
  - Did not nurture enough the relationship to have the industry division keep this project
  - Did not react at the same pace for decision-making



LIFE SUPPORT SYSTEMS SHOULD INCLUDE THE RISK OF MICROBIOLOGICAL ANTIBIOTIC RESISTANCE

- Active Microbial biomass on board
- Mutants can be selected and enriched when populations are subject to constraints (physical, chemical,…)
- Including antibiotics
- Closed systems: increased risk

ANTIMICROBIAL RESISTANCE (AMR) IS A GLOBAL PUBLIC HEALTH CONCERN



10 MILLION DEATHS

annually could be attributable to AMR in 2050, more than cancer (8.2 million)[1]

AMR DRIVERS

are well-known and can be acted upon:

1 Jim O'Neill. 2016. Tackling drug-resistant infections globally: final report and recommendations, the Review on Antimicrobial Resistance.

HOW DID WE GET THERE?

BIOMÉRIEUX

01
Overuse & misuse of antibiotics in therapy

02
Overuse & misuse in food production animals

03
Spread of resistant bacteria

04
Fewer new antibiotics

W.H.O. PRIORITY LIST OF RESISTANT ORGANISMS NEEDING NEW ANTIBIOTICS

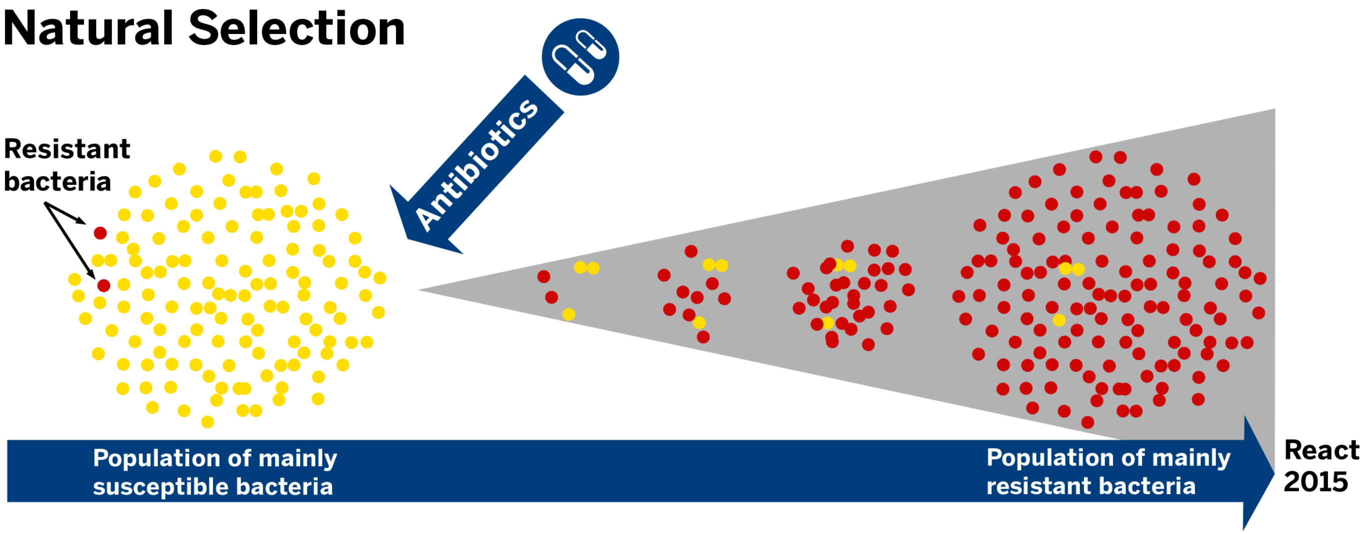
Priority 1: CRITICAL	Priority 2: HIGH	Priority 3: MEDIUM
▪ ***Acinetobacter baumannii***, carbapenem-resistant	▪ ***Enterococcus faecium***, vancomycin-resistant	▪ ***Streptococcus pneumoniae***, penicillin-non-susceptible
▪ ***Pseudomonas aeruginosa***, carbapenem-resistant	▪ ***Staphylococcus aureus***, methicillin-resistant, vancomycin-intermediate and resistant	▪ ***Haemophilus influenzae***, ampicillin-resistant
▪ ***Enterobacteriaceae***, carbapenem-resistant, ESBL-producing	▪ ***Helicobacter pylori***, clarithromycin-resistant	▪ ***Shigella spp.***, fluoroquinolone-resistant
	▪ ***Campylobacter spp.***, fluoroquinolone-resistant	
	▪ ***Salmonellae***, fluoroquinolone-resistant	
	▪ ***Neisseria gonorrhoeae***, cephalosporin-resistant, fluoroquinolone-resistant	

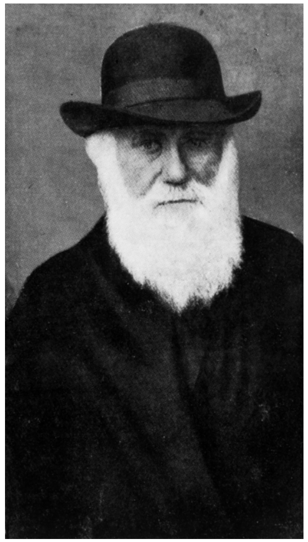
Source: WHO 2017

1. ANTIBIOTICS SELECT RESISTANT BACTERIA

Natural selection by antibiotics

Spontaneous mutations in the bacterial DNA may lead to resistance.
Antibiotics select such resistant mutants.
Antibiotic resistance appeared before man: e.g. beta-lactamases originated 2 billion years ago [1]





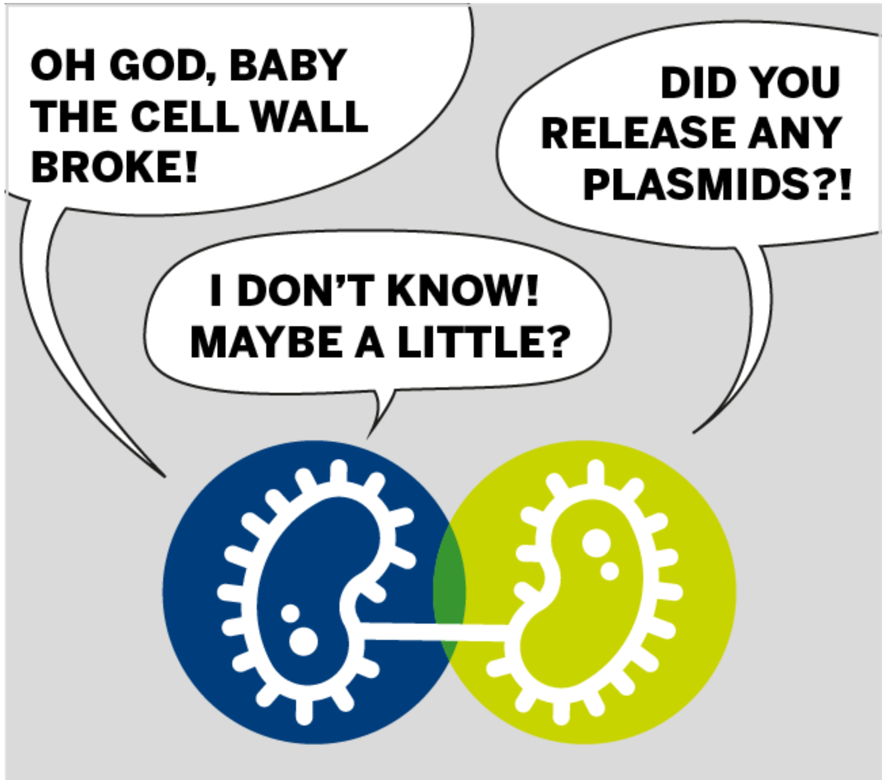
Darwin

2. RESISTANCE DETERMINANTS CAN BE TRANSFERRED

Through horizontal gene transfer to other neighboring bacteria, *e.g.*. in the human gut.

The genetic support of resistance (plasmid, transposons) can disseminate very easily.

High epidemic potential



3. THE 'SPACE-CIFITY' OF ANTIMICROBIAL RESISTANCE

- **A pool of humans**
  - having their own microbiota (gut flora, skin..)
  - Potentially reduced immune defences (space, stress)
- **A pool of bacteria, fungi**
- **A pool of antibiotics**
  - restricted on-board pharmacy
- **Spatial opportunities for interactions**
  - A closed environment with compartments favoring interactions (digestive tract, Melissa, water recycling)
  - Space conditions (radiations, μ gravity: ↗ biofilms & resistance)
- **Temporal opportunities for interactions**
  - long-haul flights

Risk assessment for selection and dissemination of resistant organisms

POTENTIAL USE-CASES

1. **An astronaut having been exposed to the same class of antibiotic within the previous 6 months** ➡ **colonized with a resistant organism: room for opportunistic infection, or for on-board dissemination**

e.g. oral fluoroquinolones : can select resistant *Enterobacterales* in urinary tract infections or other

- as classically seen with older people
- need to perform an antibiotic susceptibiity testing to switch antibiotic,
- need to know the local ecology of resistance

Mitigation: pre-boarding screening for astronauts for MDROs: MRSA, VRE, ESBL

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2. **Recycled water could concentrate active antibiotics from urine** → **Same water used in iterative Melissa loops could select resistant organisms, transfer them in the final compost: environment & food contamination**

TAKE-HOME MESSAGES

- Life support systems are key to support long-haul space flights
- It comes at the price of mastering the microbiological risk, especially for with high biomass fermenters like Melissa
- Terrestrial applications are a very good learning tool as well as offering disruptive innovations for a sustainable planet. Agility to partner with terrestrial industry is key.
- Antimicrobial resistance should no be underestimated in long-haul flights

BIOMÉRIEUX

PIONEERING DIAGNOSTICS