Azole Resistance in Aspergillus fumigatus in Iran: From Agricultural Fungicides to Clinical Failure-A one Health Perspective

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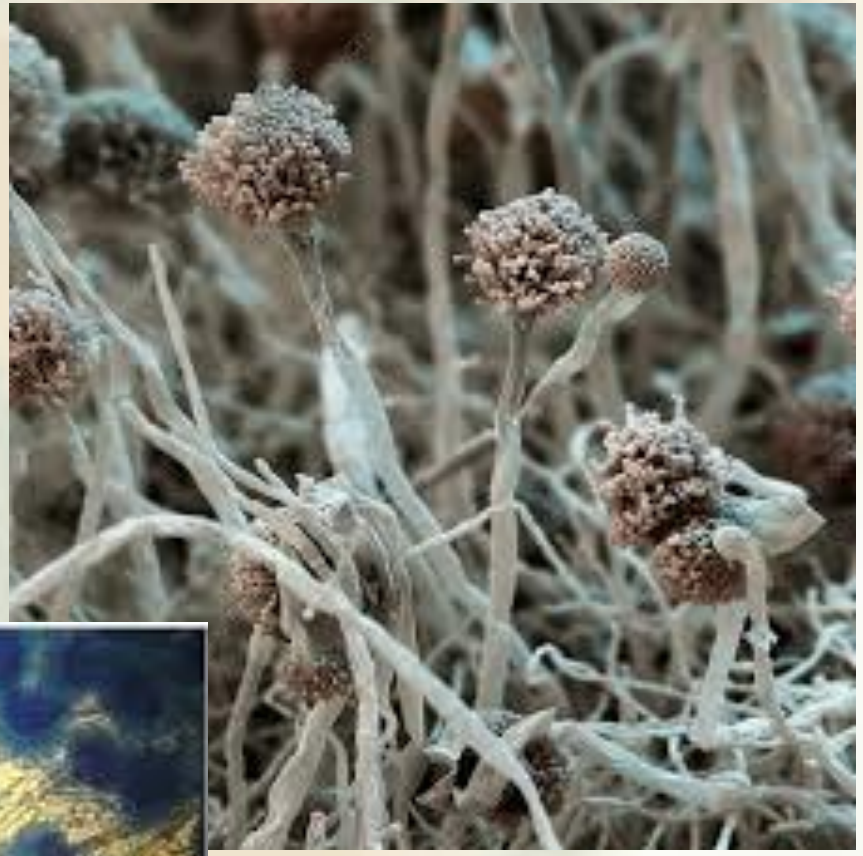
Pasteur Institute of Iran

- ***Aspergillus***

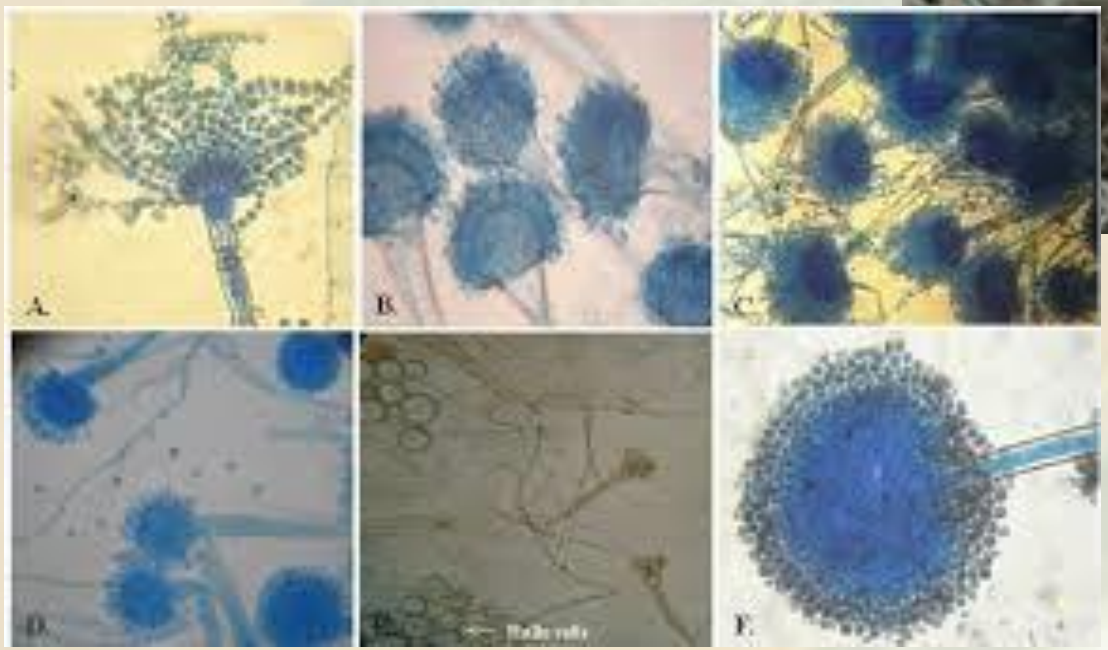
-Several hundred species

-host immunological responses

-ranging from non-invasive to chronic and invasive infection

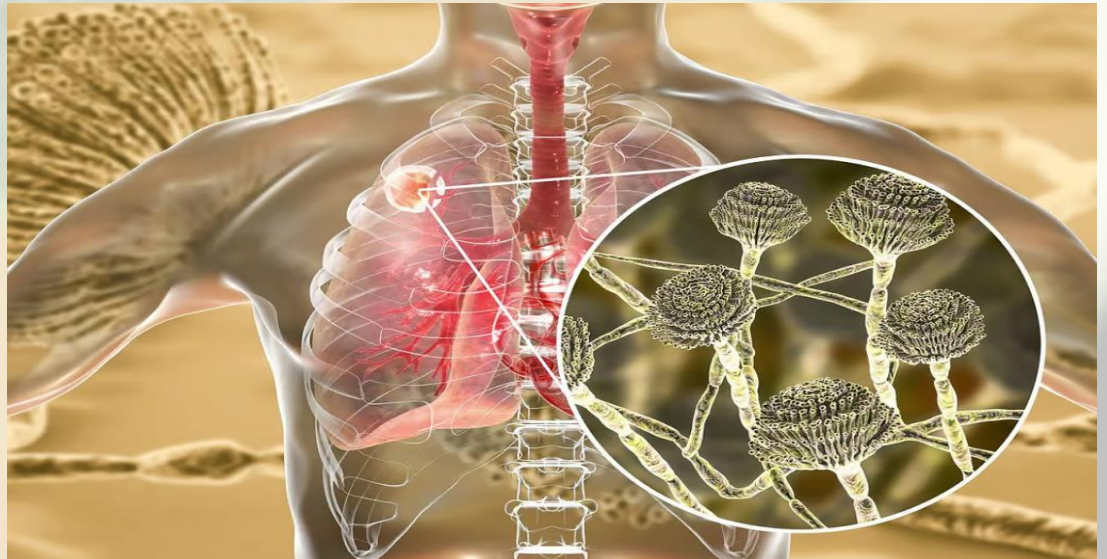






Aspergillus fumigatus — A Ubiquitous Opportunistic Mould

- **Saprophytic, thermotolerant mould (survives up to 60°C); ubiquitous due to abundant spore formation**
- **Causes a broad array of disease in humans and animals**
- **Estimated to cause >50% of the global invasive fungal disease burden**
- **Listed in the WHO Fungal Priority Pathogen List (FPPL) — critical group**
- **Presentation depends on host defense and inhaled spore load; affects immunocompetent and immunocompromised individuals**
- **Even with modern antifungal treatment, IA remains associated with high mortality**
- **IA also observed after viral respiratory infections (influenza, COVID-19) in otherwise immunocompetent individuals**
- **Take-home: *A. fumigatus* is a WHO critical-priority pathogen whose at-risk population extends beyond classic immunosuppression — vigilance is needed in SOT and post-viral patients**



The WHO Fungal Priority Pathogens List (WHO FPPL)

Critical group


Cryptococcus neoformans


Candida auris

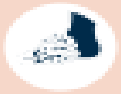

Aspergillus fumigatus


Candida albicans

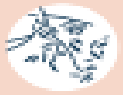
High group


Nakaseomyces glabrata (Candida glabrata)


Histoplasma spp.


Eumycetoma causative agents


Mucorales


Fusarium spp.


Candida tropicalis


Candida parapsilosis

Medium group

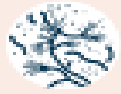

Scedosporium spp.


Lomentospora prolificans

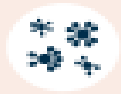

Coccidioides spp.


Pichia kudriavzeveii (Candida krusei)


Cryptococcus gattii


Talaromyces marneffei


Pneumocystis jirovecii

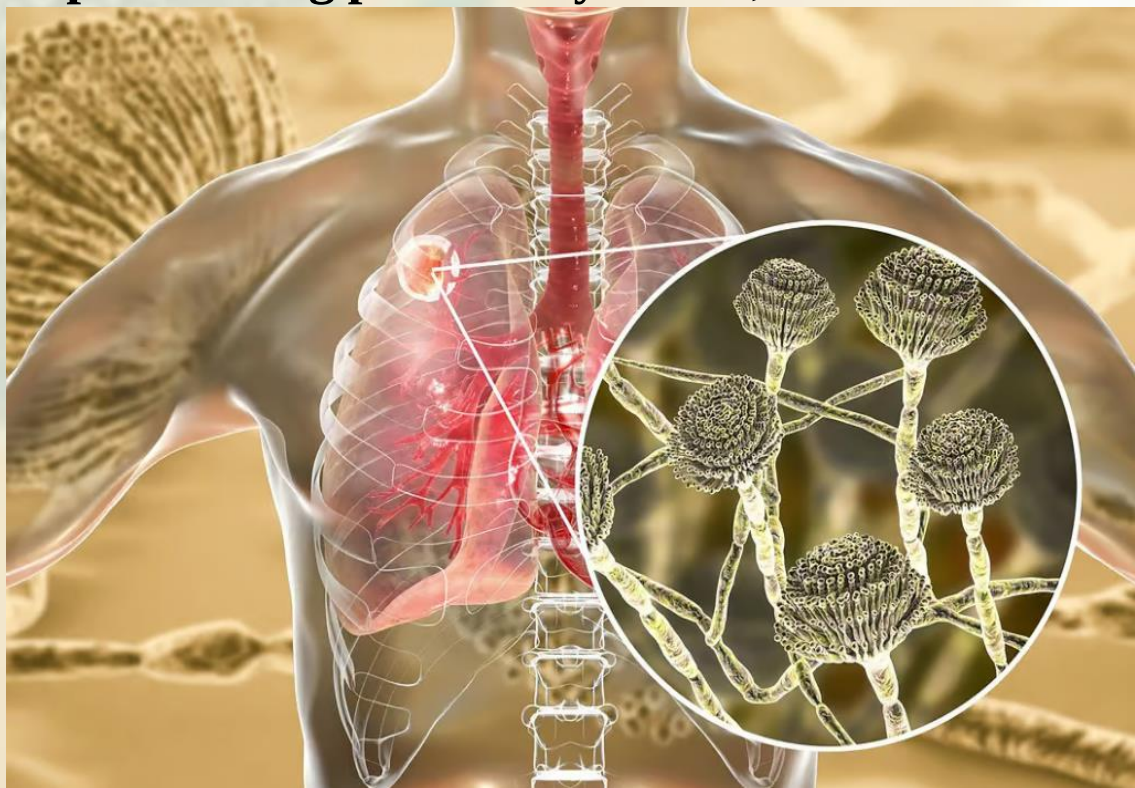

Paracoccidioides spp.

Clinical Spectrum

Category	Condition	Typical Host
Allergic	ABPA, SAFS, allergic rhinosinusitis	CF, atopic patients
Chronic	Aspergilloma; chronic pulmonary aspergillosis (CPA)	Pre-existing cavities; TB, COPD
Invasive	Invasive aspergillosis (IA)	Mainly immunocompromised

• *Aspergillosis*

- **The lower respiratory tract and lungs are the most frequently**
- **followed by the nasal sinuses and skin.**
- **Direct or hematogenous spread**
- **Cardiovascular, central nervous system**
- **The disease spectrum: immunological status, existence of pre-existing pulmonary illness,**
- **Other environmental factors which raise the spore count:**
  -reconstruction, refurbishment, and building demolition,
- **particularly in the healthcare setting can even lead to outbreaks**



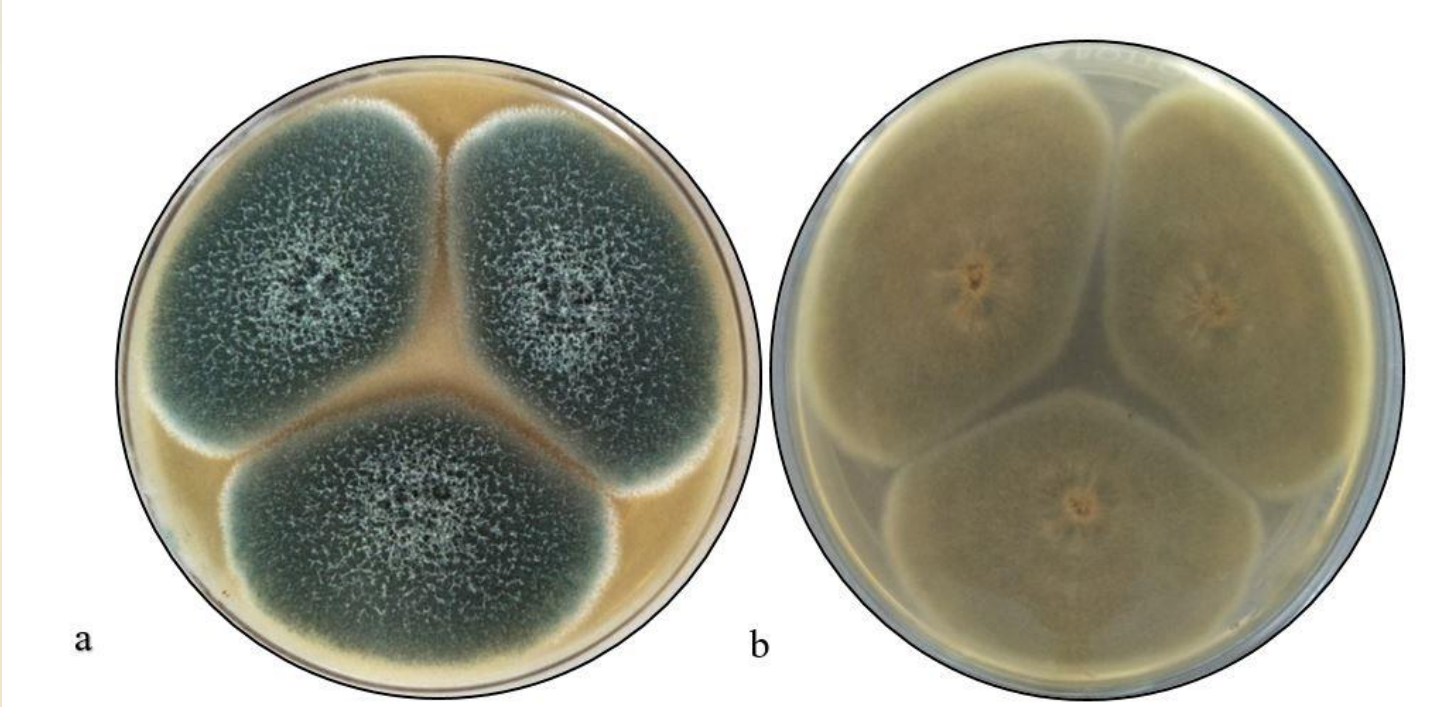
- ***A. fumigatus***

-60 to 90% of all infections

-majority of pulmonary aspergillosis

-associated with pulmonary or sinus disease in hospital settings





- ***A. flavus***

-causes around 10% of bronchopulmonary

-identified in a wide range of cases of invasive aspergillosis (IA)

-from Asia, the Middle East, and Africa.

-associated with cutaneous, mucosal, and subcutaneous tissues in hospital settings





- ***A. terreus***

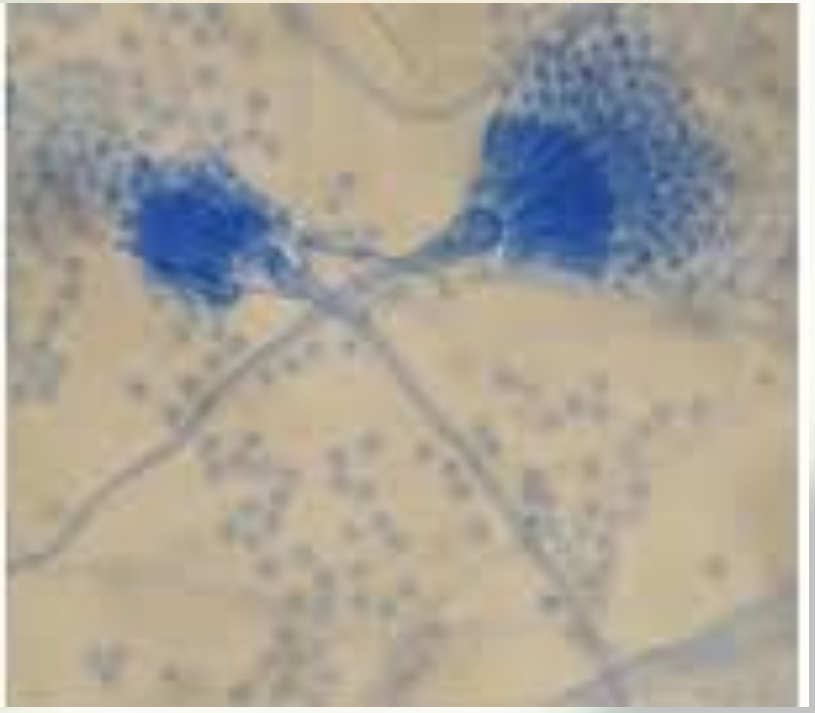
-an emerging opportunistic

-found in soil and compost,

-with an increasing clinical prevalence in recent years

- **Innsbruck, Austria, Houston, the USA, and India.**
- **Being amphotericin B resistant,**
- **nearly 4% of all IA**





- ***A. niger***

-less commonly associated with IA

-It is usually associated with otomycosis, cutaneous infections, few reports of pneumonia

-3.6% of invasive pulmonary aspergillosis (IPA)

-calcium oxalate crystals is a common indicator of infection



- ***A. versicolor***

-ubiquitous fungus

-onychomycosis, otomycosis, cutaneous infection, osteomyelitis, and ocular disease





Treatment of Aspergillusis & the Challenge of Azole Resistance

- **Current First-Line Treatment: Azoles**
- Azoles inhibit the **ergosterol biosynthesis pathway**, disrupting fungal cell membrane integrity
- **Only oral anti-Aspergillus agents available** → critical for long-term treatment (e.g., CPA) and prophylaxis
- **Two new oral antifungals** awaiting regulatory approval:
  - Olorofim
  - Manogepix
  - Both show activity against ARAf (azole-resistant *A. fumigatus*)

• Azoles in Clinical Use

- *A. fumigatus* is **intrinsically resistant to fluconazole** → only **4 azoles** used clinically
- All available in **oral and IV** formulations:

Azole	Primary Use
Itraconazole	CPA treatment
Voriconazole	CPA treatment; **first-line IA therapy**
Isavuconazole	**First-line IA therapy**
Posaconazole	Prophylaxis & salvage therapy (high-risk patients: AML, HCT, SOT)

• The Growing Problem: Acquired Azole Resistance

- Azole resistance in *A. fumigatus* is **progressively increasing** → major clinical concern
- Recommend **abandoning azole monotherapy** when resistance rates **exceed 10%**
- Alternative options:
  - **Azole–echinocandin combination therapy**
  - **Liposomal Amphotericin B (AmB)**

Table 1. Typical susceptibility pattern of cryptic species within the *Aspergillus fumigatus* complex

Cryptic species	*In vitro* susceptibility pattern		Cryptic species	*In vitro* susceptibility pattern	
Aspergillus lentulus	Amphotericin B	R	*Aspergillus thermomutatus / Aspergillus pseudofischeri*	Amphotericin B	S
	Itraconazole	R		Itraconazole	R
	Posaconazole	R		Posaconazole	R
	Voriconazole	R		Voriconazole	R
Aspergillus fumigatiaffinis	Amphotericin B	R	*Aspergillus hiratsukae*	Amphotericin B	S
	Itraconazole	R		Itraconazole	S
	Posaconazole	R		Posaconazole	S
	Voriconazole	R		Voriconazole	S
Aspergillus udagawae	Amphotericin B	R	*Aspergillus fumisynnematus*	Amphotericin B	S
	Itraconazole	S		Itraconazole	S
	Posaconazole	S		Posaconazole	S
	Voriconazole	S		Voriconazole	S
Aspergillus viridinutans	Amphotericin B	S	*Aspergillus oerlinghausenensis*	Amphotericin B	S
	Itraconazole	R		Itraconazole	S
	Posaconazole	R		Posaconazole	S
	Voriconazole	R		Voriconazole	S

Breakpoints for susceptibility testing of *A. fumigatus* according to EUCAST: susceptible (S): MIC $\leq$ 1 mg/l for AmB, ITR and VOR; MIC $<$ 0.125 mg/l for POS. Resistant (R): MIC $>$ 1 mg/l for AmB, ITR and VOR; MIC $>$ 0.25 mg/l for POS.

Antifungal Susceptibility *Aspergillus fumigatus* complex

- ***A. fumigatus* sensu stricto** (the main species): Susceptible to triazoles (except fluconazole) and amphotericin B (AmB)
- **Cryptic species have different patterns:**
  - *A. lentulus*, *A. fumigatiaffinis*, *A. udagawae* → **High MIC for AmB**
  - *A. lentulus*, *A. fumigatiaffinis* → **High MIC for triazoles**
  - *A. udagawae* → Intermediate voriconazole, low itraconazole/posaconazole
  - *A. viridinutans*, *A. thermomutatus* → **Azole-resistant, AmB-susceptible**
  - *A. oerlinghausenensis*, *A. hiratsukae*, *A. fumisynnematus* → **Susceptible to azoles and AmB**

Mechanisms underlying azole resistance in *Aspergillus fumigatus*

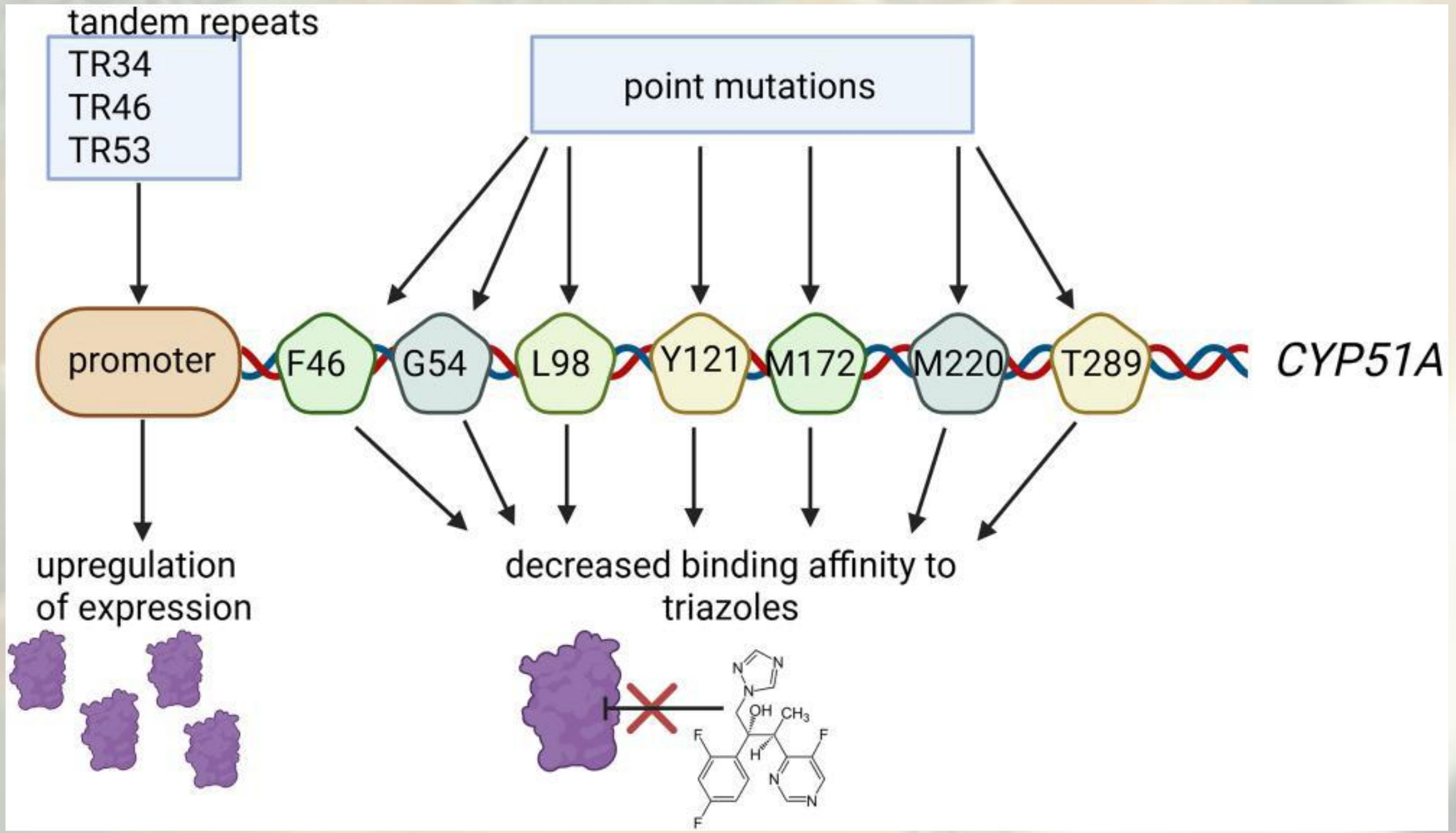
- **Route 1: Patient (In-Patient) Route**
- Caused by **long-term azole exposure** in patients
- Primarily seen in **lung cavities** (aspergilloma, CPA, CF)
- Requires **asexual reproduction** → unlikely in acute IA unless cavitary lesion develops
- **Mechanisms:**
  - Point mutations in **CYP51A** gene (e.g., G54, M220) → alter azole binding
  - Increased **cyp51A expression**
  - Increased **efflux pump activity**
  - Non-cyp51A mechanisms

- **Route 2:Environmental Route (Dominant)**
- Caused by exposure to **agricultural azole fungicides**
- **Mechanisms:**
  - **TR34/L98H** and **TR46/Y121F/T289A**
  - Tandem repeat (34/46 bp) in promoter → **upregulated cyp51A**
  - Point mutations (codons 98, 121, 289) → **reduced azole affinity**
- Possibly fueled by **MSH6 mutations** (DNA mismatch repair) → higher mutation rates

- **Why the Environmental Route Dominates**
- Found in **80–90% of clinical isolates** in the Netherlands
- Resistant conidia inhaled → germinate under azole pressure → IA
- **Virulence** of resistant strains ≈ wild-type
- Cross-resistance from agricultural fungicides (difenoconazole, tebuconazole, epoxiconazole)

Two Routes of Resistance Development

Route	Driver	Key Features
Environmental (dominant)	Agricultural azole fungicides	Sexual reproduction important; infections even in patients without risk factors; 80–90% of Dutch clinical isolates
In-patient	Long-term medical azole exposure	Lung cavities (aspergilloma, CPA, CF); asexual reproduction; unlikely in acute IA unless cavitary lesion

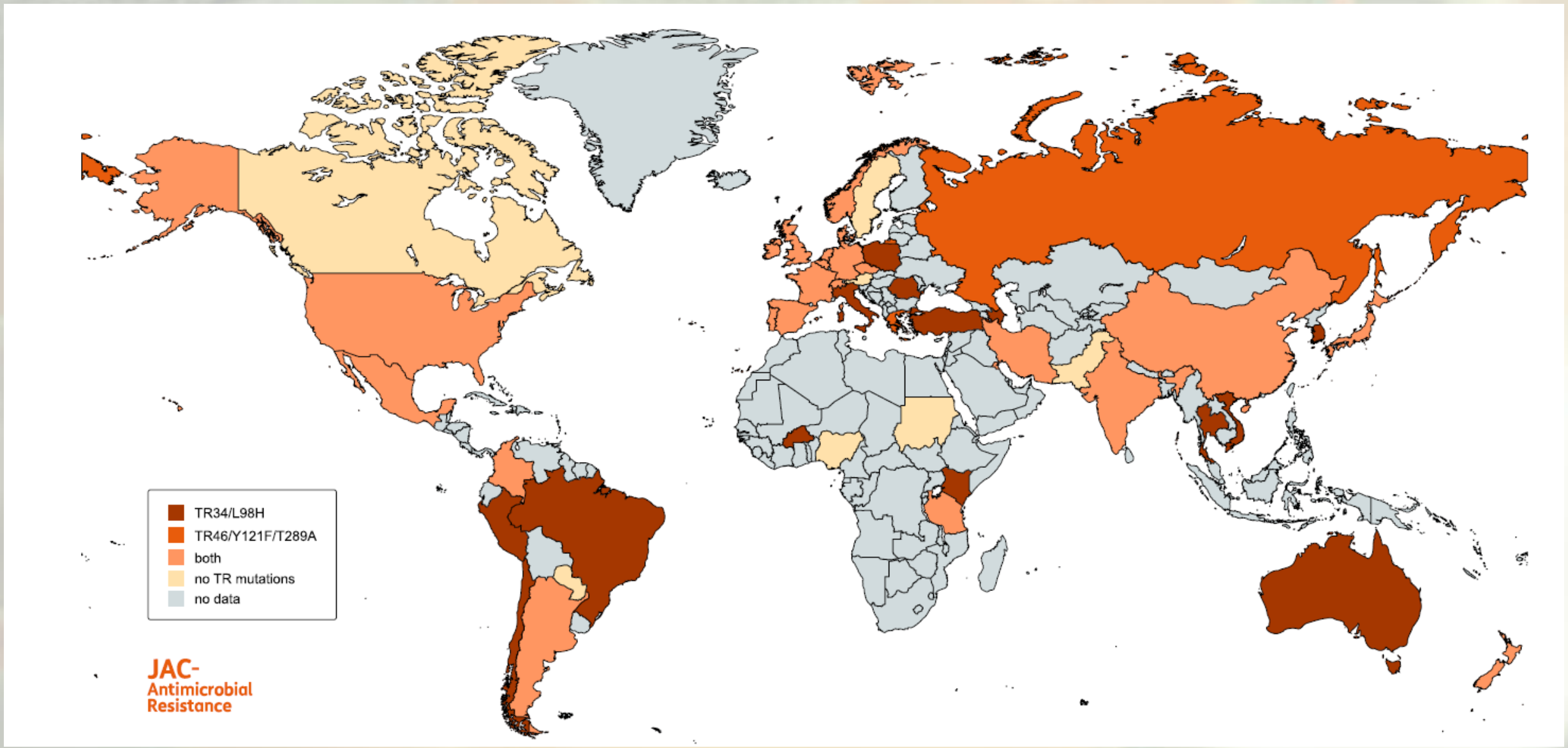

tandem repeats
TR34
TR46
TR53
point mutations
promoter
F46
G54
L98
Y121
M172
M220
T289
CYP51A
upregulation
of expression
decreased binding affinity to
triazoles
N
N
N
OH
CH3
H
F
F
F
N
N

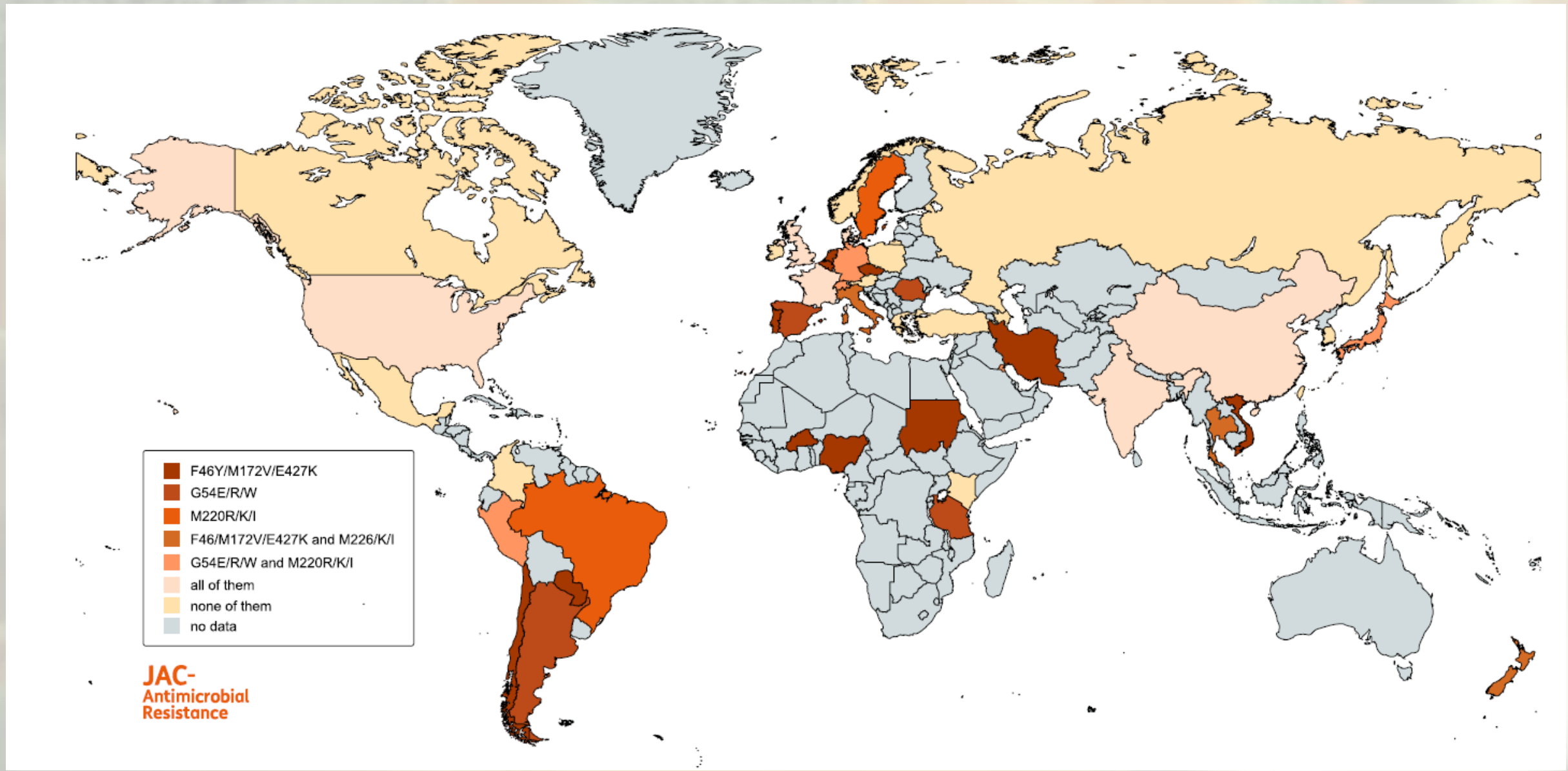
Key Resistance Mechanisms (CYP51A)

Mechanism	Effect
TR34/L98H (dominant)	Resistance to **medical + agricultural** azoles (both alterations needed)
TR46/Y121F/T289A	Highly resistant to **voriconazole**; itraconazole variable
G54E/R/W, P216L	High MIC: itraconazole & posaconazole; voriconazole less affected
G138, G448	**Multi-azole resistant**
F291I, D262Y, F46Y/M172V/N248T/D255E/E427K	Voriconazole resistance (some also in susceptible strains)
Non-CYP51A	Increased efflux pump activity; other mechanisms

Table 2. Global prevalence of azole-resistant *Aspergillus fumigatus* and date of first sample from which ARAf was isolated

Country	Resistance mechanism	Isolation of oldest known ARAf strain	Source of first isolate	Year of report
North America				
Canada	Non-cyp51A-related	2002	C	2020
Mexico	TR_{34}/L98H	2014–2017	C	2019
	TR_{46}/Y121F/T289A	Not provided	E	2021
	Non-cyp51A-related	Not provided	E	2021
USA	Not determined	1980s	C	1997
	TR_{34}/L98H	2010	C	2016
	TR_{46}/Y121F/T289A	2008	C	2016
	Other cyp51A mutations	2001	C	2016
Iran	TR_{34}/L98H	2003–2009	C + E	2013
	TR_{46}/Y121F/T289A	2017–2018	E	2020
	Other cyp51A mutations	2016–2021	C + E	2022
	Non-cyp51A-related	2016–2021	C + E	2022
	TR_{53}	2015	E	2016
Paraguay	Other cyp51A mutations	Not provided	E	2021
Peru	TR_{34}/L98H	2016–2017	C	2020
	Other cyp51A mutations	2016–2017	C	2020
Asia				
Azerbaijan	TR_{34}/L98H	2017–2019	C	2025
	Non-cyp51A-related	2017–2019	C	2025
China	TR_{34}/L98H	2008–2009	C	2011
	TR_{46}/Y121F/T289A	2013	C	2015
	Other cyp51A mutations	2002–2003	C	2005
India	TR_{34}/L98H	2008–2009	C	2012
	TR_{46}/Y121F/T289A	2012–2013	E	2014
	Other cyp51A mutations	2013	C	2015


TR34/L98H
TR46/Y121F/T289A
both
no TR mutations
no data
JAC-
Antimicrobial
Resistance


F46Y/M172V/E427K
G54E/R/W
M220R/K/I
F46/M172V/E427K and M226/K/I
G54E/R/W and M220R/K/I
all of them
none of them
no data
JAC-
Antimicrobial
Resistance

Global Epidemiology of Azole-Resistant *A. fumigatus* (ARA)

Year / Period	Key Milestone / Event
Late 1980s	First ARAf strains (USA/California); itraconazole resistance.
1997	Earliest European isolates (Netherlands, Sweden, France).
1998	Italy, Japan (G54 mutation).
2003	China (TR34/L98H documented).
2005	Taiwan (TR34/L98H documented).
2007	TR34/L98H mechanism discovered → later found worldwide.
Since then	TR46/Y121F/T289A, TR53, TR120, and evolving variants (e.g., TR34/R65K/L98H).

Azole-Resistant *A. fumigatus* (ARAf) in Iran

Year	Key Milestone / Event
2005	First **TR34/L98H** mutation documented in Iran (also the first TR mutation reported globally in the literature).
2013	Environmental study confirming TR34/L98H in Iranian *A. fumigatus* isolates.
2020	First **TR46/Y121F/T289A** isolates reported in Iran.

Azole-Resistant *A. fumigatus* (ARAf) in the Middle East & Iran — Regional & National Surveillance

Middle East Regional Picture (environmental ARAf isolates)

Resistance mechanism	Frequency
TR34/L98H	**37.1%**
TR46/Y121F/T289A	**1.9**

Metric	Value
ARAf frequency (combined clinical + environmental)	**16.1–16.2%**
Resistant isolates	**78 / 483 tested**
Regional standing	Among **higher-prevalence** countries in Middle East / West Asia
Historical significance	**World's first documented TR34/L98H mechanism (2005)**

Iran — Key National Data (2016–2021, 5-year surveillance)

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Original Article

Meta-analysis of antifungal resistance patterns of *Aspergillus* species in Iran

Pooled Resistance Rates — *A. fumigatus*

Antifungal	Resistance Rate
Amphotericin B	6.97%
Caspofungin	1.40%
Itraconazole	17.61%
Posaconazole	4.56%
Voriconazole	14.68%

Pooled Resistance Rates — *A. flavus*

Antifungal	Resistance Rate
Amphotericin B	13.16%
Caspofungin	13.09%
Itraconazole	10.19%
Posaconazole	1.23%
Voriconazole	0.58%

Conference Abstract Free

Azole-Resistant Aspergillus fumigatus in Patients with Cystic Fibrosis, a Prospective Study

Atefeh Fakharian | Azadeh Bandegani | Soheila Khalilzadeh | Hamid Badali See Less

European Respiratory Journal 2025 66(suppl 69): PA3974; DOI: https://doi.org/10.1183/13993003.congress-2025.PA3974

- ***Aspergillus* species — most prevalent (55.1%)**
- **14 isolates of *A. fumigatus* phenotypically azole resistant (9%)**
- One isolate carried **multiple mutations**
- **Two new SNPs identified: I242V and D490E**
- **Routine antifungal susceptibility testing** is essential in CF management

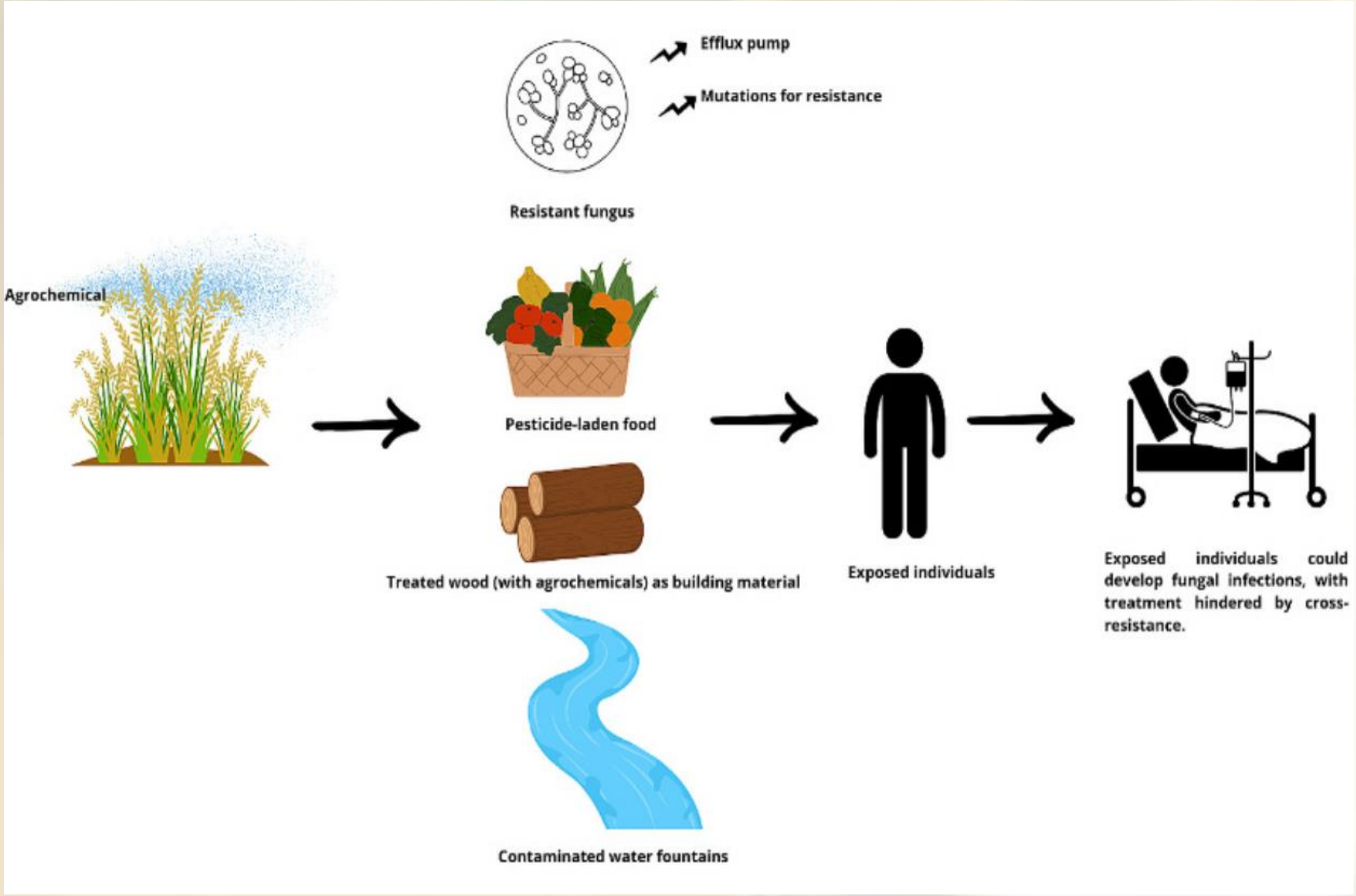
Improve the overall response to priority fungal pathogens and prevent the development of antimicrobial resistance

- Three Primary Areas for Action:
- 1. Strengthening Laboratory Capacity & Surveillance
- 2. Sustainable Investments in Research, Development, and Innovation
- 3. Public Health Interventions

Fungicides

Antifungal drug resistance has increased due to the emergence of antifungal-resistant strains.

use of fungicides in agricultural practice is probably an important cause.



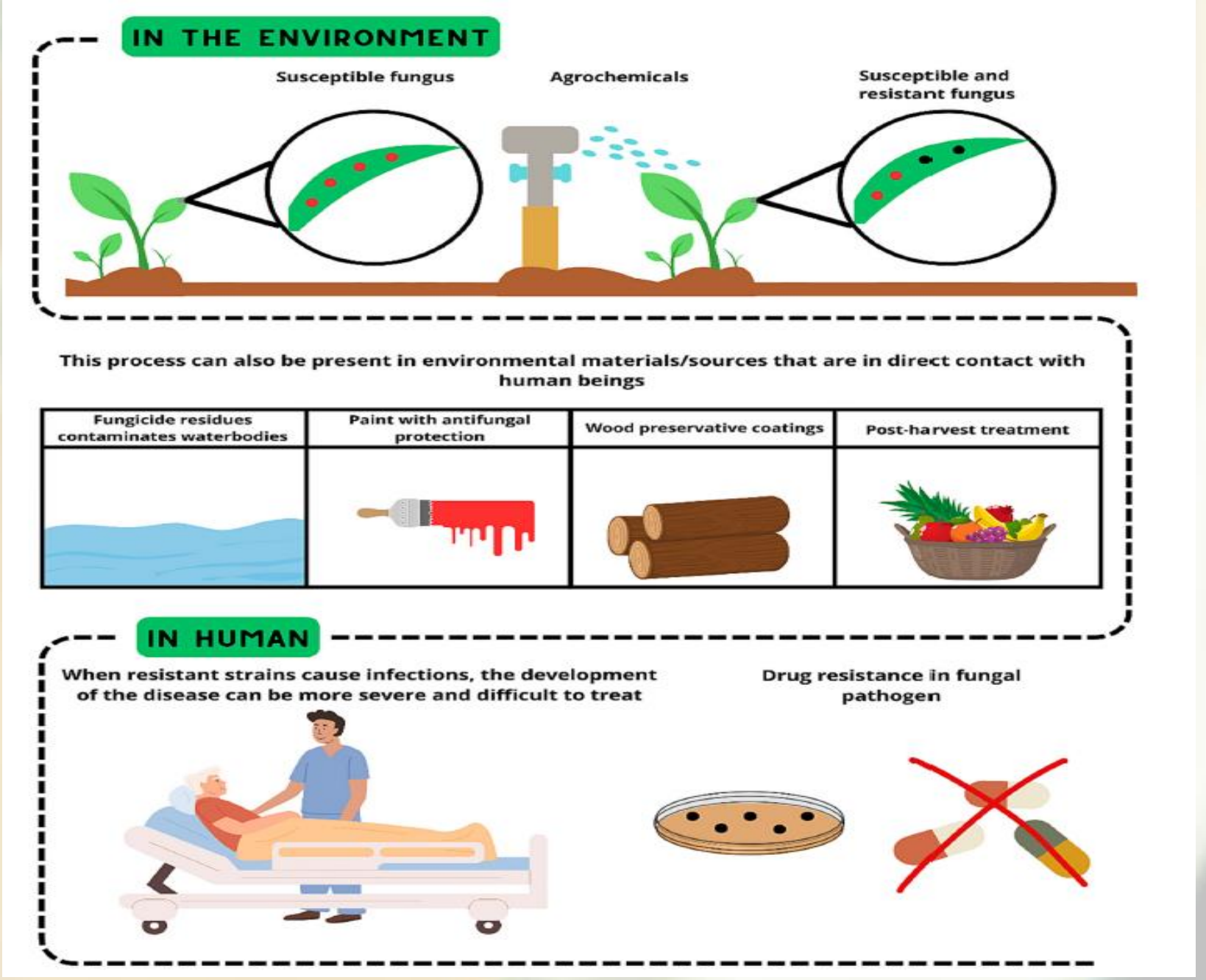
Environmental fungicides promote cross-resistance to clinical antifungals.

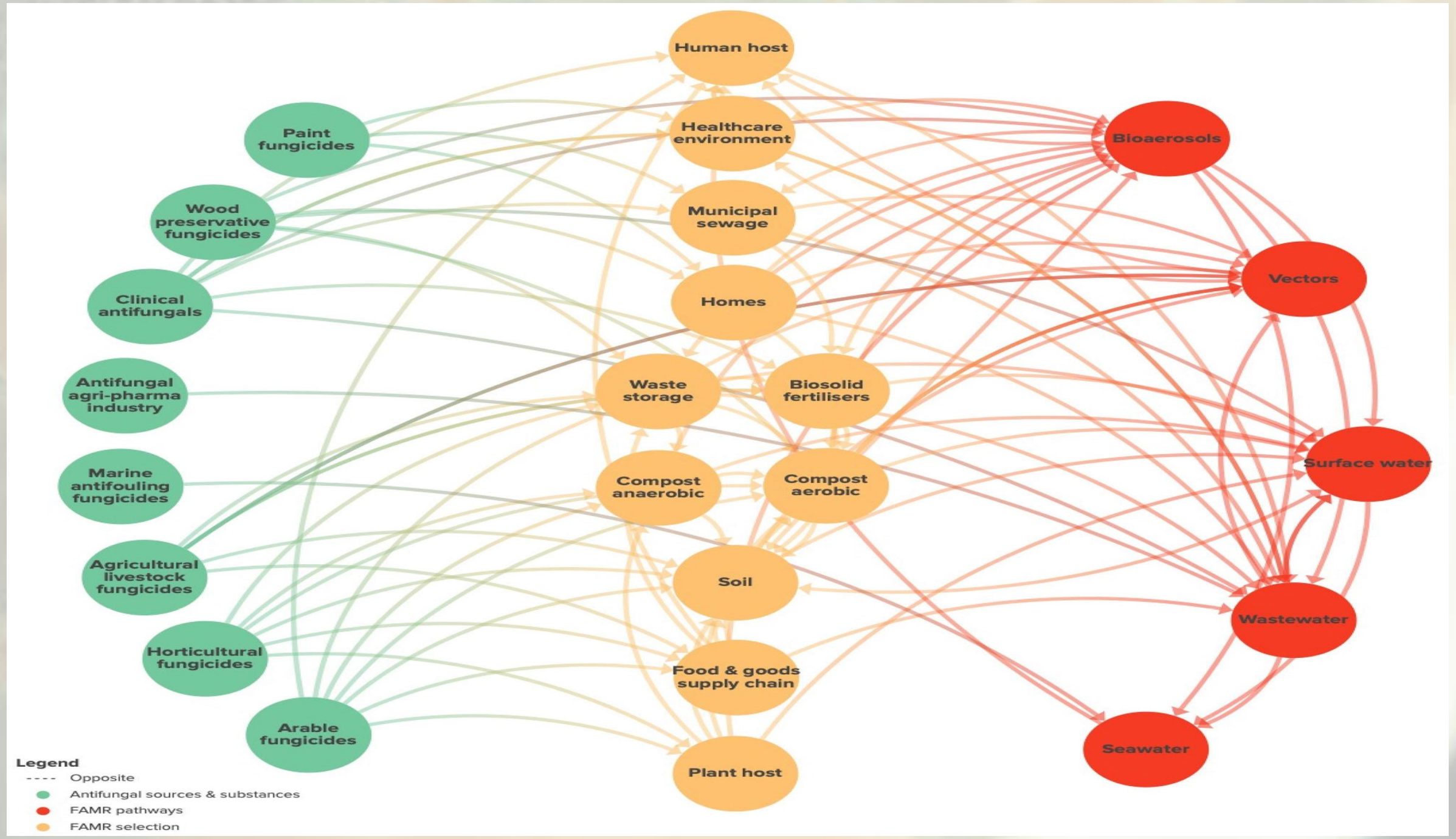
In antifouling agents for watercraft to prevent biofilm buildup.

In 'antimould' paints available in home improvement stores.

As components in wood preservatives in the timber industry.

For protecting plant bulbs in horticulture via dipping or spraying.




Human host
Healthcare environment
Municipal sewage
Homes
Waste storage
Biosolid fertilisers
Compost anaerobic
Compost aerobic
Soil
Food & goods supply chain
Plant host
Paint fungicides
Wood preservative fungicides
Clinical antifungals
Antifungal agri-pharma industry
Marine antifouling fungicides
Agricultural livestock fungicides
Horticultural fungicides
Arable fungicides
Bioaerosols
Vectors
Surface water
Wastewater
Seawater
Legend
Opposite
Antifungal sources & substances
FAMR pathways
FAMR selection

• History of fungicides :

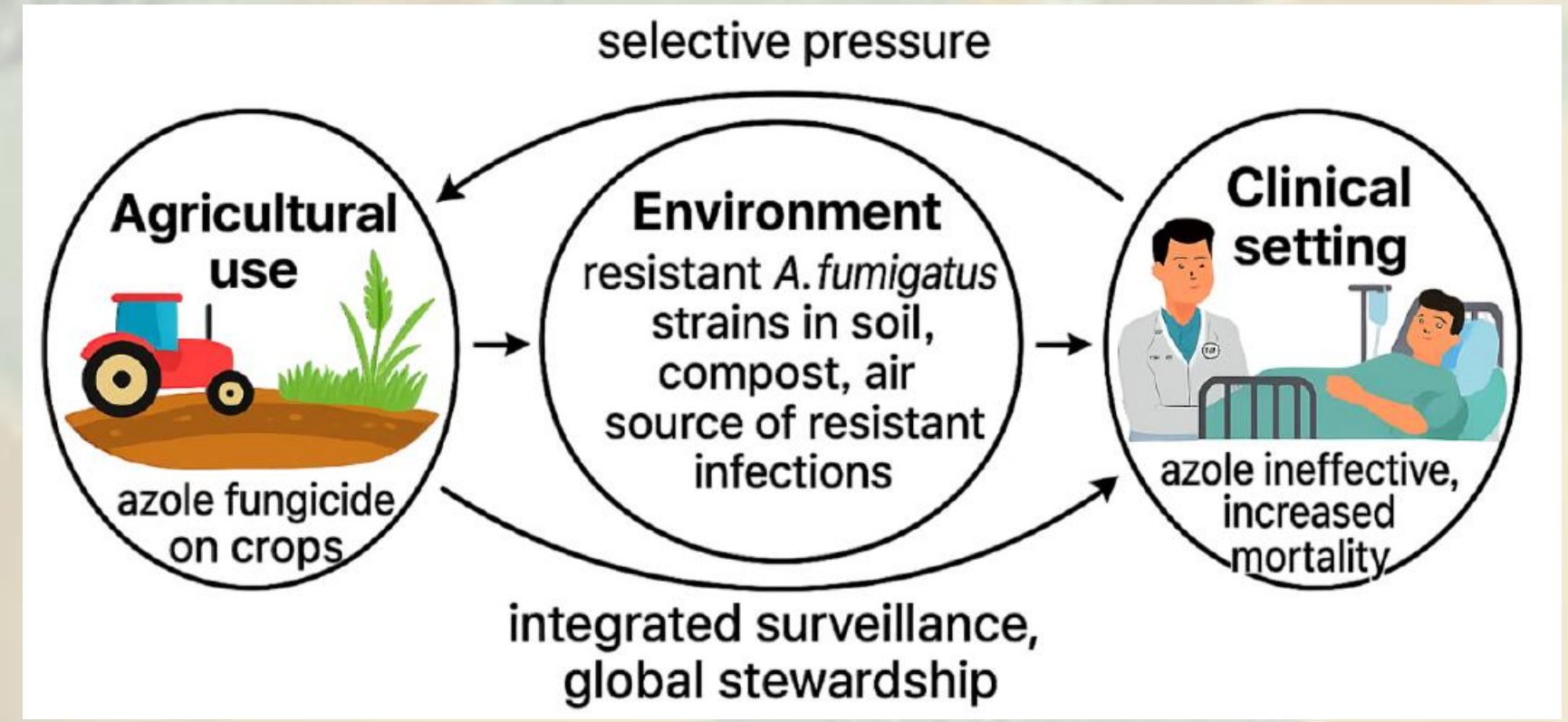
- In the 1950s, the first fungicides were discovered,
- Early chemical controls, inorganic compounds, copper sulphate and sulphur,
- Mid-20th century organic fungicides (e.g., dithiocarbamates), low resistance risk, lacked effects, leading to bans of some (e.g., mancozeb).
- In the 1960s, site-specific fungicides like benzimidazoles, systemic action, quickly faced resistance.
- In the 1970s, azoles, curative power, but resistance developed due to CYP51 mutations, (clinical triazole drugs in the 1980s)
- The 1990s, strobilurins targeting mitochondrial respiration, yet resistance spread rapidly.
- Newer classes, SDHIs and QoIs have precise modes of action, cross-resistance with important medical antifungals such as olorofim.
- Five classes represent ~62 % (US $21.18 billion in 2024) of the worldwide use,

sterol biosynthesis inhibitor (SBI), succinate dehydrogenase inhibitors (SDHIs), quinone outside inhibitors (QoIs), β-tubulin inhibitors and multisite fungicides

Table 1 | Main modes-of-action (MOAs) of antifungal chemicals in the clinic and the environment, and where dual-use may occur

MOAs (FRAC code)	Class	Examples		Dual use
		Clinical	Agricultural	
Demethylation Inhibitors (DMIs) of fungal membrane sterol biosynthesis (G)	Azoles	Imidazole	Imazalil Prochloraz	Yes
	Triazoles	Fluconazole Itraconazole Voriconazole Posaconazole Isavuconazole	Tebuconazole Tetraconazole	Yes
		Opelconazole (*in development*)	Piperazines	Possible
		-	Pyridenes	No
		-	Pyrimidines	No
		- -	Triazolinthiones	No
	Allylamine	Terbinafine		
Cell wall biosynthesis (H)	Echinocandins	Caspofungin Micafungin Anidulafungin Rezafungin	-	No
	Carboxylic acid amides	-	Mandipropamid	No
	Triterpene	Ibrexafungerp		
Cell membrane disruption (F)	Polyenes	Amphotericin Nystatin	-	No
	Phosphorothiolates	-	Iprobenfos	No
Nucleic Acids metabolism (A)	Pyrimidine analogues/ Phenylamides	Flucytosine Tavaborole	Metalaxyl	Possible
	DHODH inhibition	Olorofim (*in development*)	Ipflufenoquin Quinofumelin	Possible
Cytoskeleton and motor proteins (B)	MBC fungicides	-	Benomyl	No
Respiration (C)	Succinate dehydrogenase inhibitors	-	Fluxapyroxad Boscalid	No
	Quinone outside inhibitors	-	Azoxystrobin	No
Protein transfer	GWT-1 inhibition	Fosmanogepix (*in development*)	Aminopyrifen (*in development*)	Possible

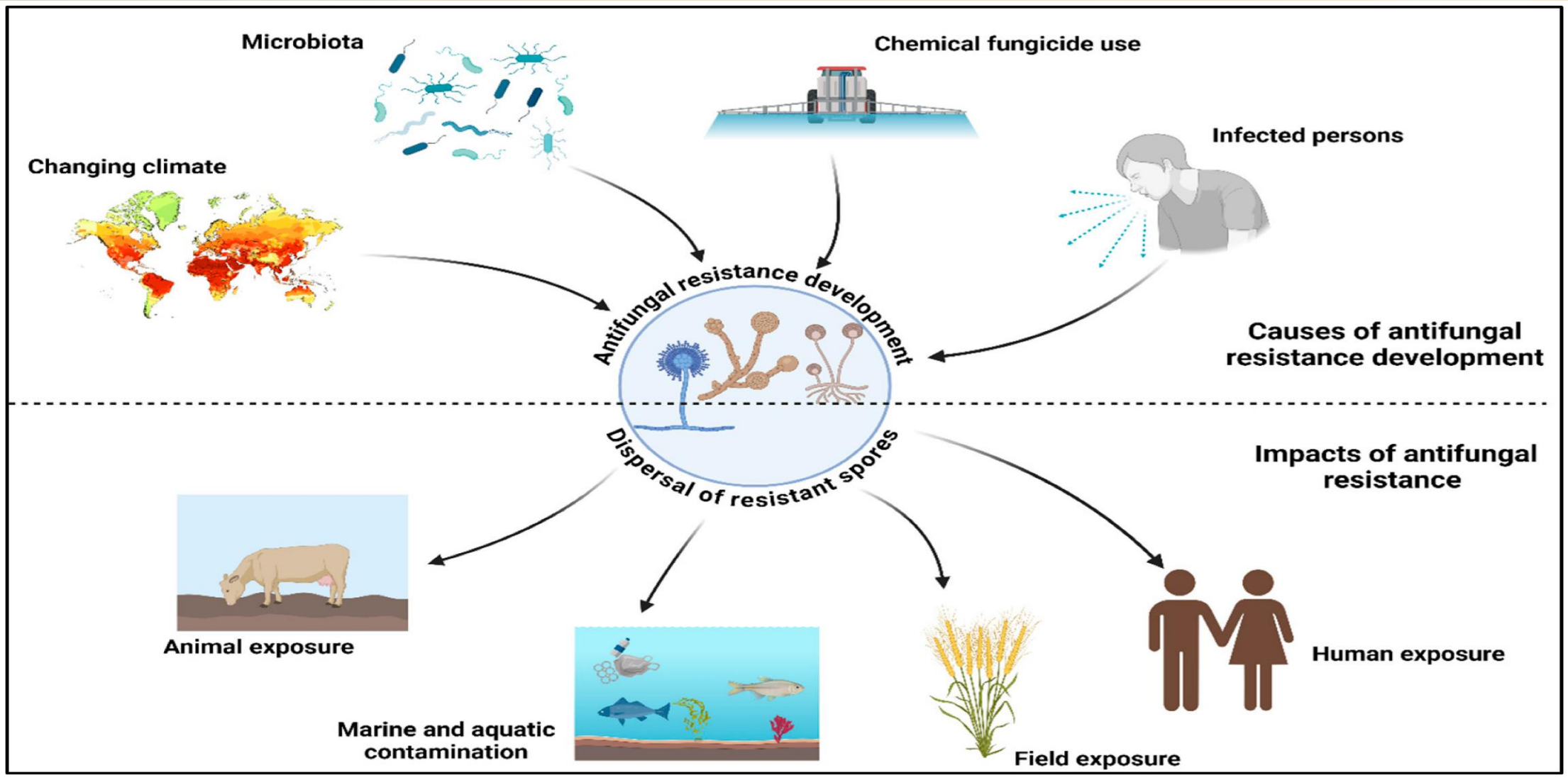
The list of agricultural fungicide MOAs is limited to the main widely-used categories, with the full list accessible at[9].



the “One Health” model of antifungal resistance.

Agricultural azole use, environmental selection of resistant *Aspergillus fumigatus* strains, and clinical outcomes

Antifungal medications enter the environment through various pathways




What we can do???

Anti-resistance strategies

• Dosage,

-High doses, reduce population size,

-sublethal doses, increase resistance via stress mutations

-higher doses promote resistance by selecting existing mutations

-Though the ideal dose is debated, reducing total applications while ensuring control

• Timing

-Fungicides used preventatively stop infections

-while curative use treats established ones.

-fungicides should be applied only after disease detection or damage thresholds curative treatments require higher doses, increase resistance risk, are becoming less effective, especially in Z. tritici.

• Mixture or alternations

-Refrain from applying fungicide with single mode of action.

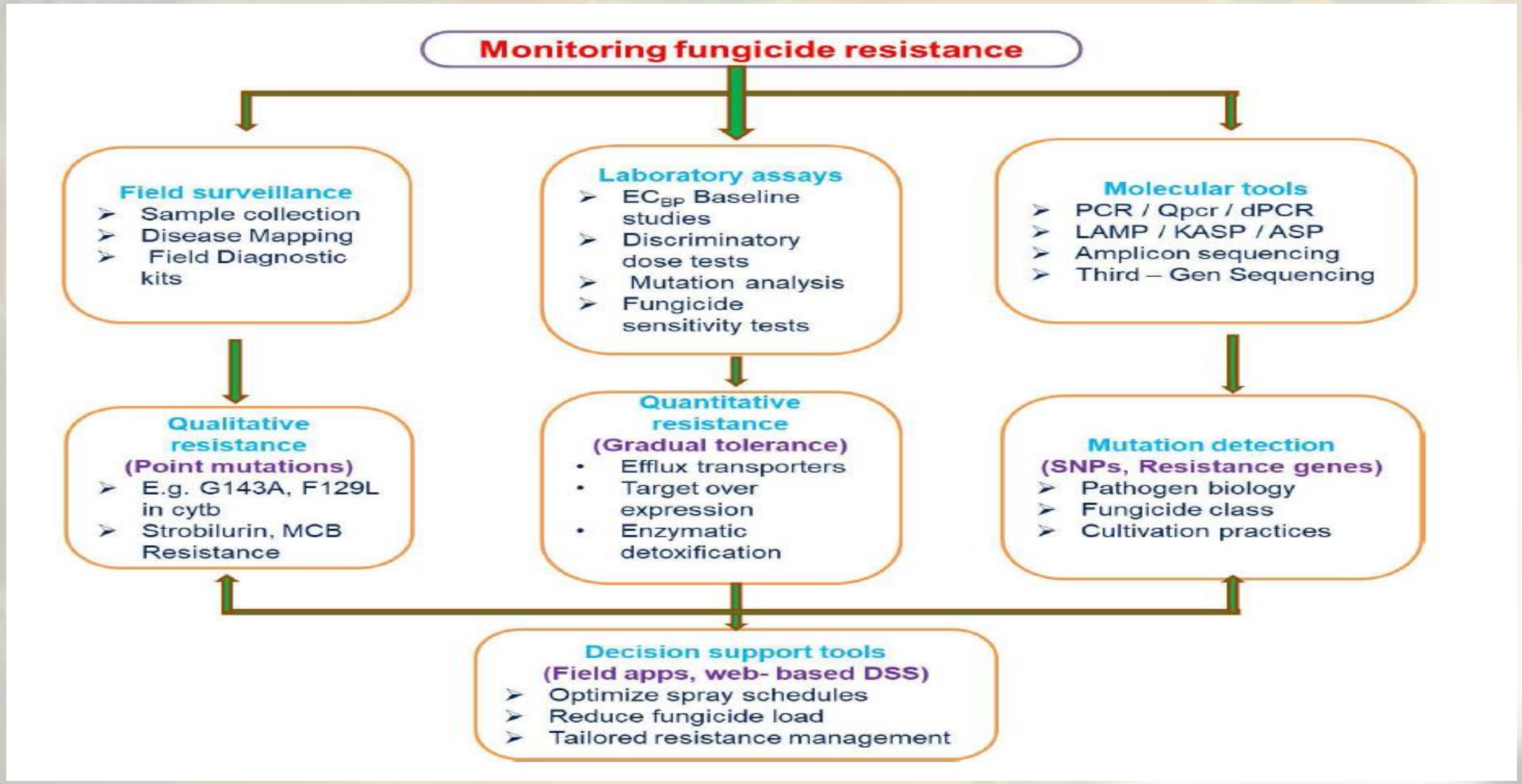
-Applies mixture of fungicides with two or more distinct mode of action

- **The advantages:**

-When resistant strains remain susceptible to another mode, growth differences shrink, reducing resistance pressure.

- Each mixture component can be applied at lower rates without losing effectiveness.

Monitoring Fungicide Resistance


Monitoring fungicide resistance
Field surveillance
Sample collection
Disease Mapping
Field Diagnostic kits
Laboratory assays
EC_{BP} Baseline studies
Discriminatory dose tests
Mutation analysis
Fungicide sensitivity tests
Molecular tools
PCR / Qpcr / dPCR
LAMP / KASP / ASP
Amplicon sequencing
Third – Gen Sequencing
Qualitative resistance
(Point mutations)
E.g. G143A, F129L in cytb
Strobilurin, MCB Resistance
Quantitative resistance
(Gradual tolerance)
Efflux transporters
Target over expression
Enzymatic detoxification
Mutation detection
(SNPs, Resistance genes)
Pathogen biology
Fungicide class
Cultivation practices
Decision support tools
(Field apps, web- based DSS)
Optimize spray schedules
Reduce fungicide load
Tailored resistance management

Monitoring Fungicide Resistance

- **Establishing Sensitivity Baselines,** by measuring EC_{50} values

-*Fusarium graminearum*

- **Field-kit Based Techniques for Detection of Azole Fungicides**

-brown rot (*Monilinia fructicola*)

- **Internet-supported Surveillance Systems (DSSs)**

-*Alternaria alternate, Fusarium graminearum,…*

- **Molecular Diagnostics (PCR, qPCR, Sequencing)**

-*Erysiphe necator* and *Blumeria graminis* f. sp.

- **LAMP-Based Techniques**

-*Botrytis cinerea*, *Cercospora beticola*, *Podosphaera xanthii*

- **Bioinformatics and Genomic Tools for Monitoring**

-*A. fumigatus* and *Zymoseptoria tritici*

Resistance Management Strategies for Azole Fungicide

Developing of new fungicides

Fungicide	Novel Mode of Action	Crop/Disease Focus	Status	References
Gilboa™	Nucleic acid metabolism inhibitor	Cereals (Septoria, Sclerotinia)	Registration pending (UK/EU)	[196]
Adapzo Active	HDAC inhibitor	Soybean (Asian Soybean Rust)	Submission in South America	[197]
Fenpicoxamid	Complex III inhibitor (QiI)	Cereals, sugar beet, fruits	Registered/marketed	[198]
Florylpicoxamid	QiI derivative	Cereals, fruits	Field trials / evaluation	[198]
Quinofumelin	Dihydroorotate dehydrogenase (DHODH) inhibitor	Fusarium, cereal/root pathogens	Under study (no cross-resistance)	[199]
Metyltetraprole	TetrazolinoneQoI (subgroup 11A)	Alternaria, resistant pathogens	Marketed (no QoI cross-res)	[200]
Pyrazole amide S26	Dual-action—PAMP + plant defense	Botrytis, fungal foliage diseases	Lab promising, early stage	[201]

Future Direction for Fungicide Resistance

1-Socioeconomic Impacts

2-Environmental Impacts

- **Socioeconomic Impacts:**

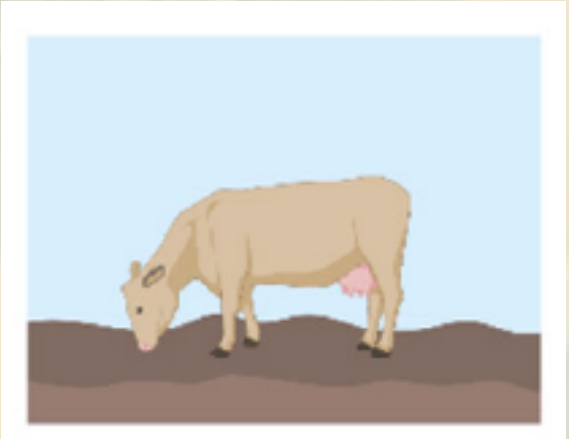
-Reduced crop yields and quality

- **Lower photosynthesis efficiency,**
- **premature plant death and incomplete grain or fruit development**
- **yield losses of 20-50%**



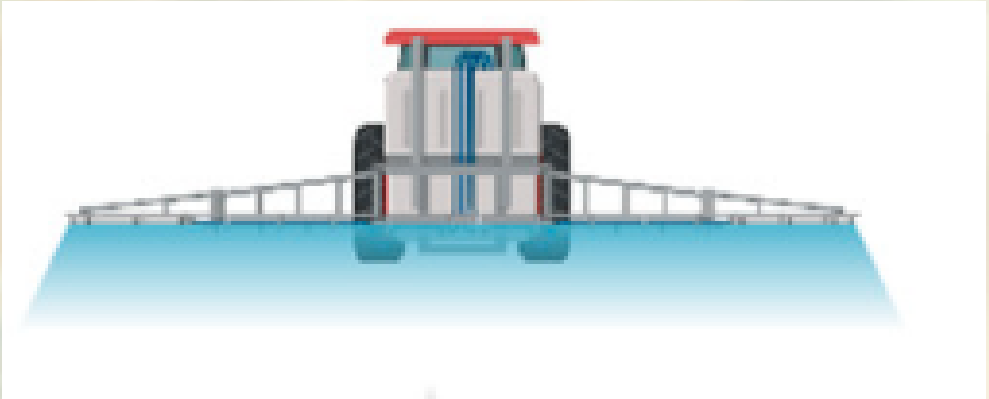
-Increased production costs

- **higher input costs**
- **increased labour expenses**
- **reduced marketable yield**
- **lower quality produce**
- **Indirect cost of resistance**





• Environmental Impacts:



• Escalated chemical use

-Application frequency

- dosage levels

- multiple or more potent fungicides

-Broader chemical spectrum

- fungicide mixtures

- Overall chemical load

• Soil and water contamination

- higher doses, multiple fungicides

- accumulation of residues

- non-target effects

- Simultaneous application of fungicides

- toxic effects on aquatic organisms

- persistence of fungicide residues

• Biodiversity loss

-higher doses or more frequent applications

- beneficial fungi

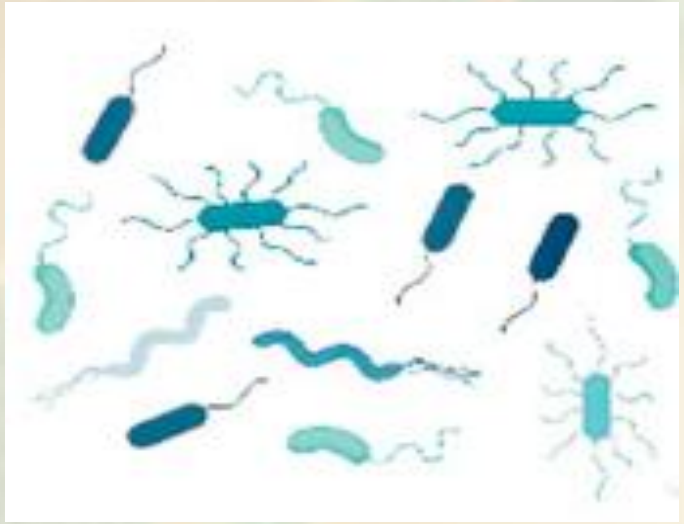
- soil bacteria

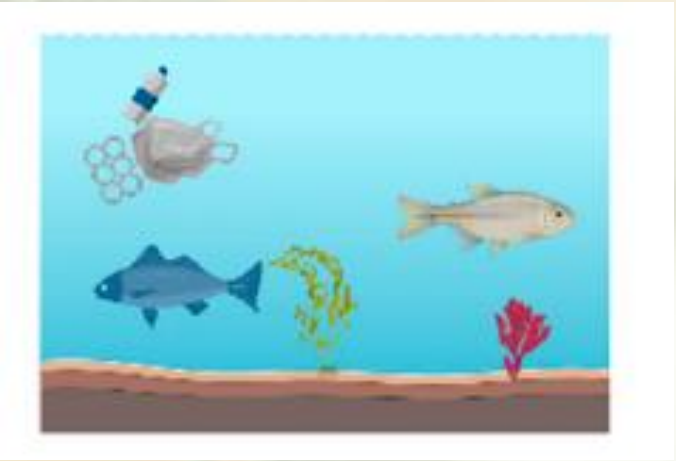
- pollinators and insects

- alters soil microbial communities

- algae and aquatic fungi

- Amphibians and invertebrates





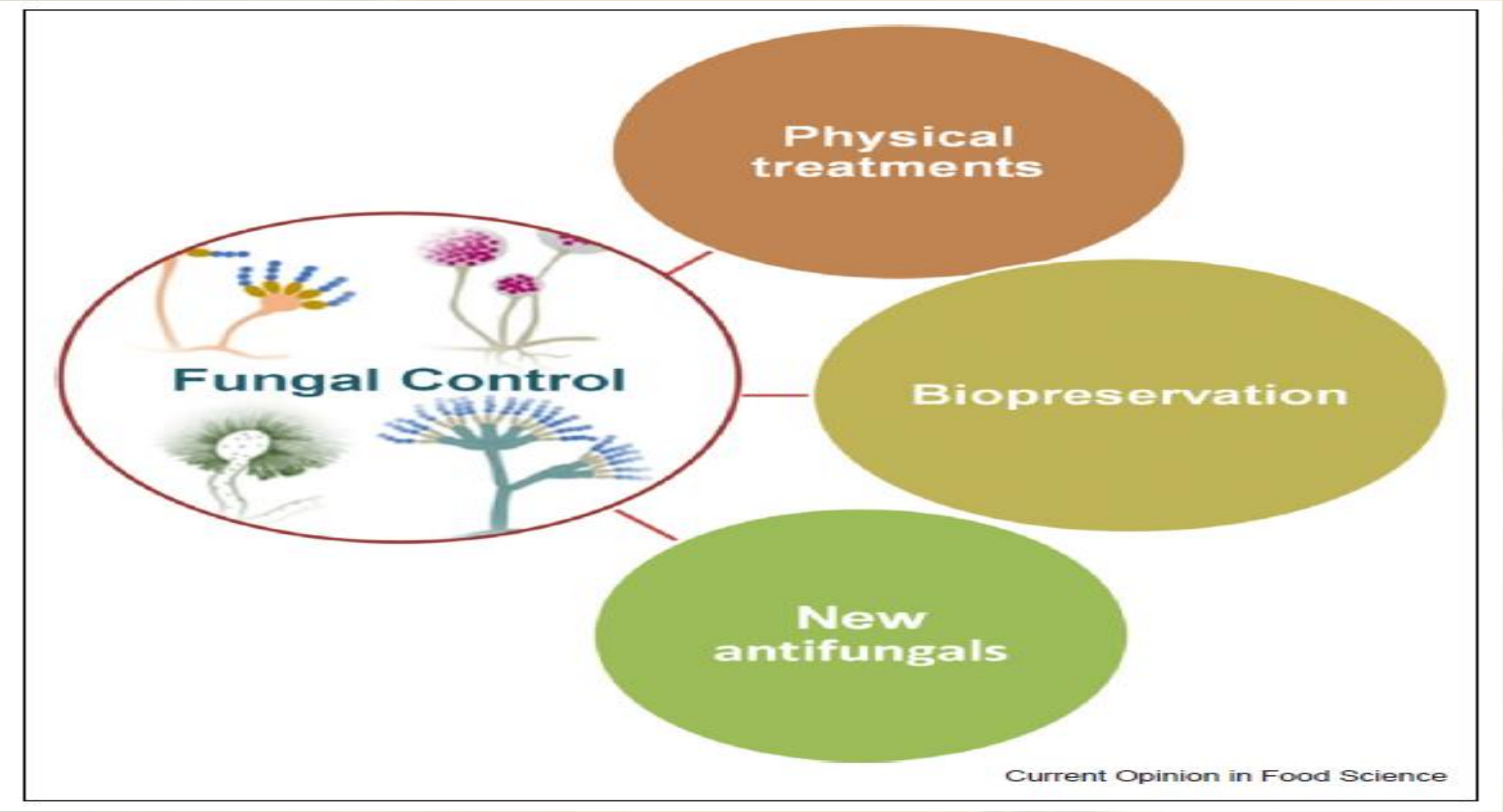
Integration of Digital Agriculture and AI in Decision-making

Tool / Platform	Region / Developer	Key Features	Role in Resistance Mitigation	APA Reference
Agro Advisor	India (Dhole Patil College of Engineering)	ML-based DSS using soil nutrients and weather data	Optimizes fungicide timing and dosage to reduce overuse	[224]
Crop In	India (Agri-tech startup)	AI + IoT platform for real-time crop and disease monitoring	Enables targeted fungicide use, minimizing blanket applications	225
Fasal	India	Sensor-based microclimate monitoring with AI-driven advisories	Predicts disease onset, reducing unnecessary fungicide sprays	[226]
Xarvio® FIELD MANAGER	Europe (BASF)	AI-powered crop health monitoring and spray optimization	Promotes mode-of-action rotation and precision fungicide application	[227]
RIM pro	Europe (Private developers)	Web-based DSS for fruit crop disease forecasting	Supports fungicide rotation and timing to delay resistance	[227]
Agro Climate DSS	USA (University of Florida)	Climate-based disease forecasting and decision support	Schedules fungicide use based on risk models, reducing resistance pressure	[227]
Plant Village Nuru	Global (Penn State University)	AI app for disease diagnosis via smartphone images	Early detection reduces reliance on curative fungicide treatments	[226]

Impact of Fungicide Resistance on Human Health

Human pathogen	WHO priority	Landscape occurrence	Landscape reproduction	Landscape transmission	Potential route for resistance to evolve in the landscape and transfer to humans
Aspergillus fumigatus	Critical	High	Sexual + asexual	High	Yes
Aspergillus fumigatus	Critical	High	Sexual + asexual	High	Yes
Fusarium fujikuroi	High	Medium	Sexual + asexual	High	Yes
Fusarium oxysporum	High	Medium	Asexual	High	Yes
Fusarium solani	High	Medium	Sexual + asexual	High	Yes
Histoplasma capsulatum	High	Medium	Asexual	High	Yes
Mucor circinelloides	High	High/medium	Asexual	High	Yes
Rhizopus oryzae (=*R. arrhizus*)	High	High/medium	Asexual	High	Yes
Scedosporium apiospermum	High	High/medium	Asexual	High	Yes

Potential control strategies



Physical treatments

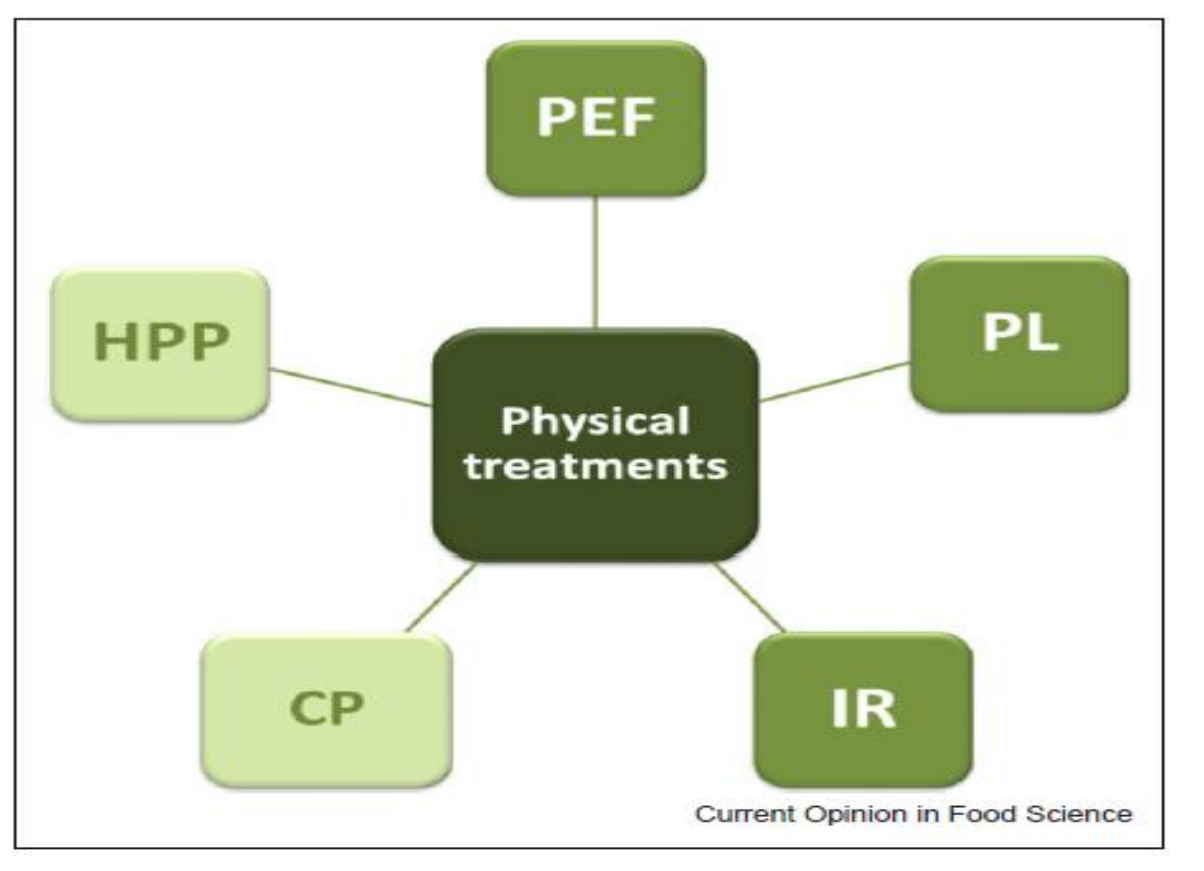
ionizing and nonionizing irradiation (IR),

high pressure processing (HPP),

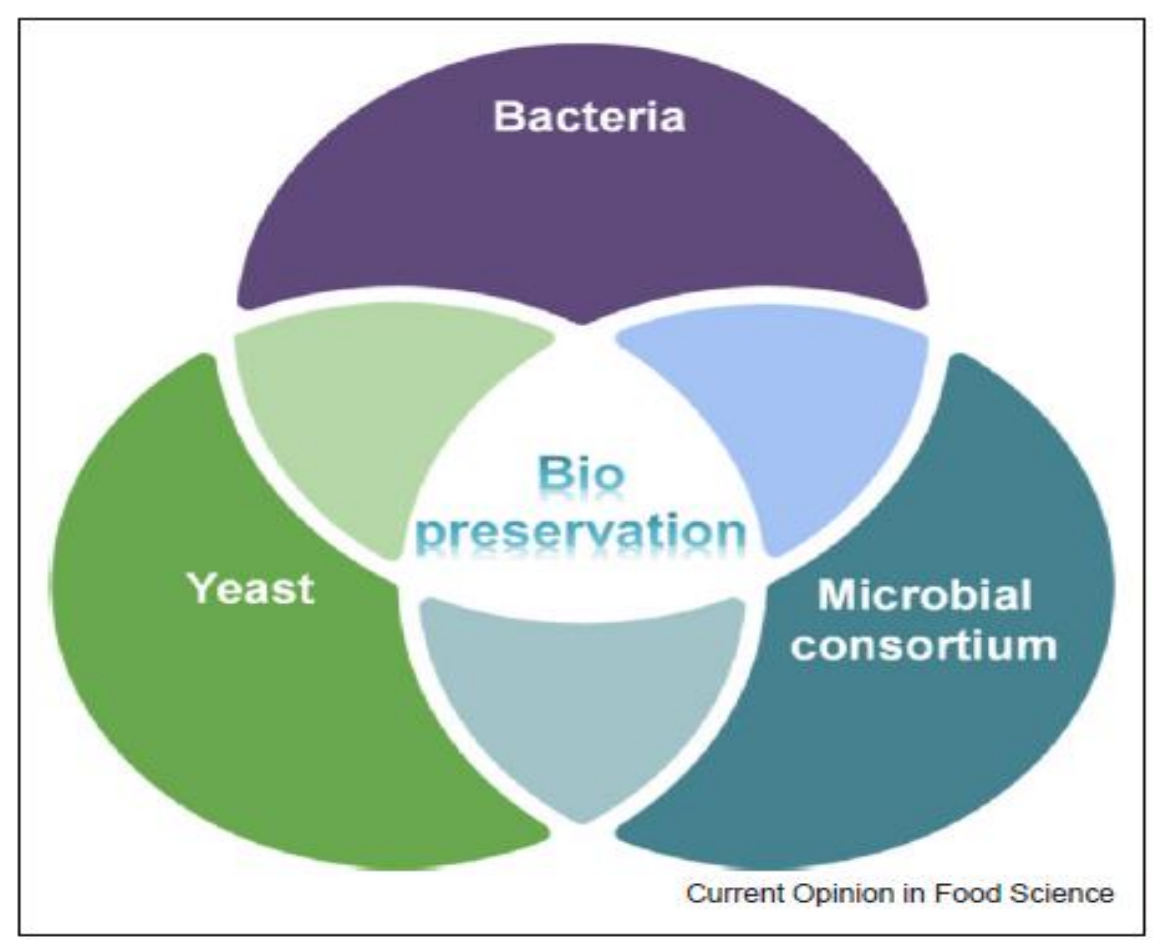
pulsed electric field (PEF),

pulsed light (PL),

cold plasma (CP)



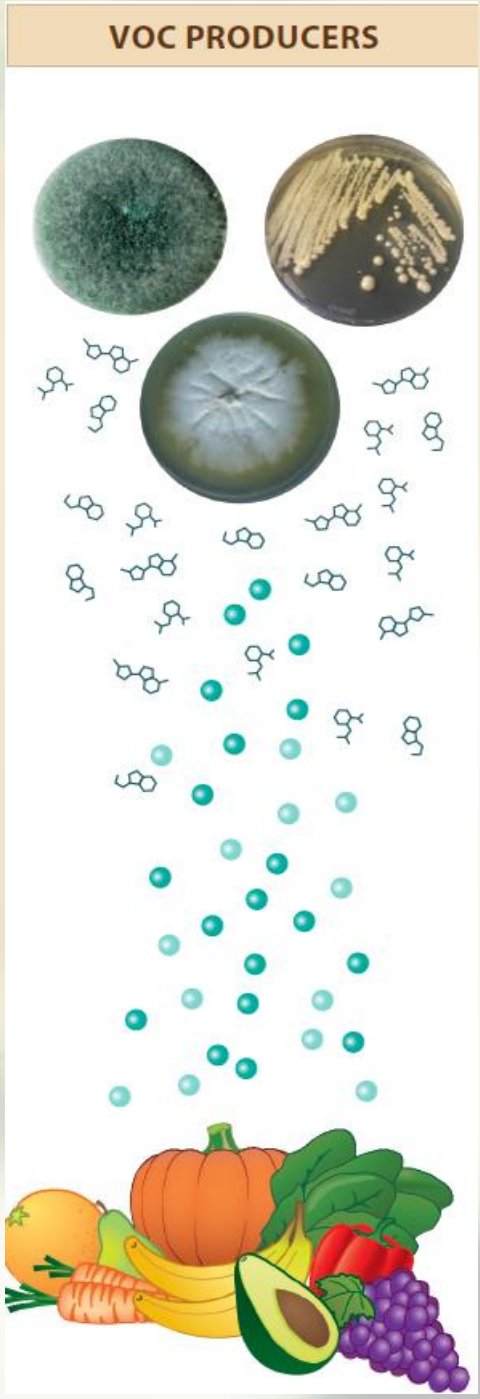
Biopreservation



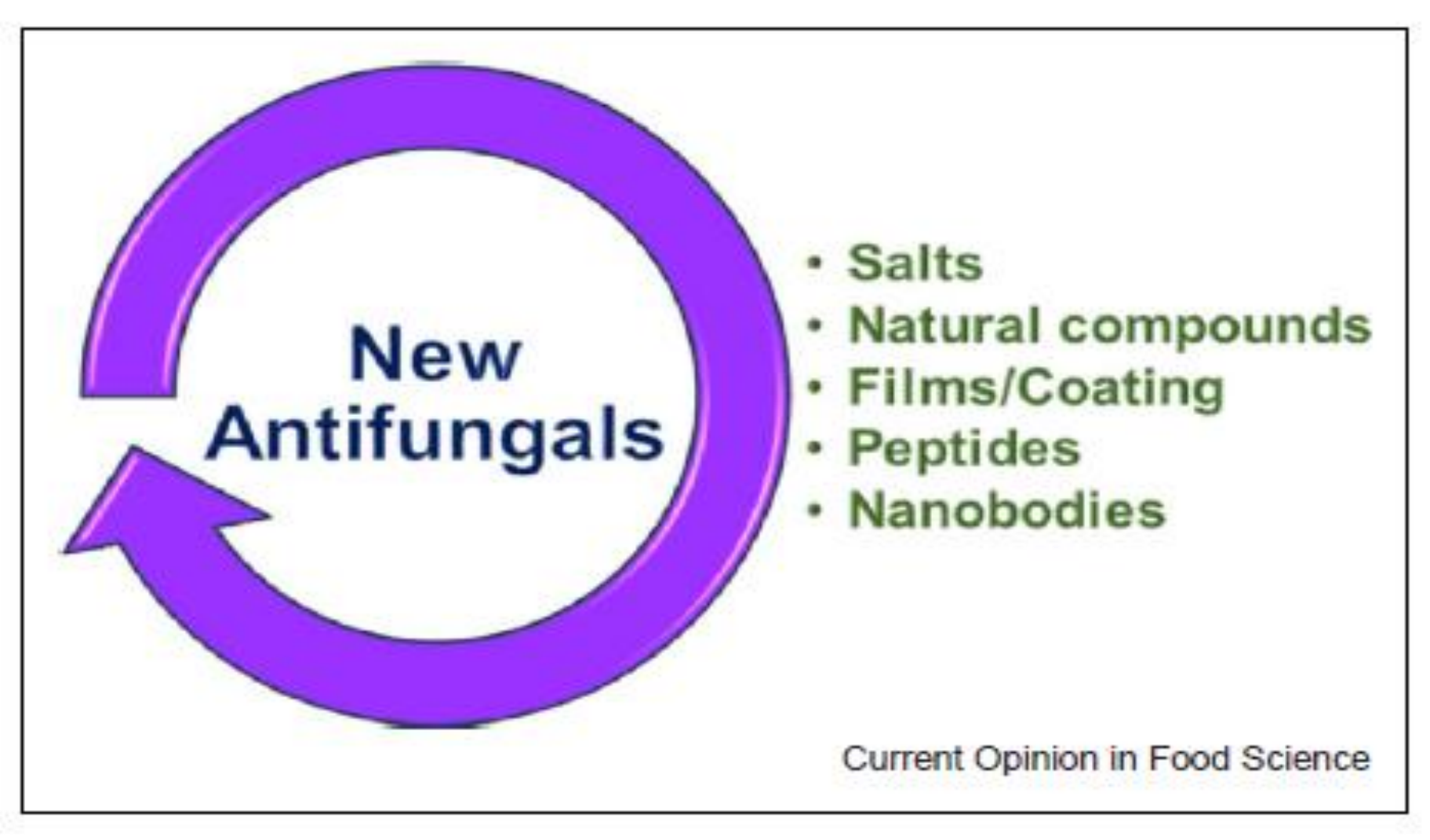
Antagonistic yeast

Central role in the biocontrol of storage pathogens.

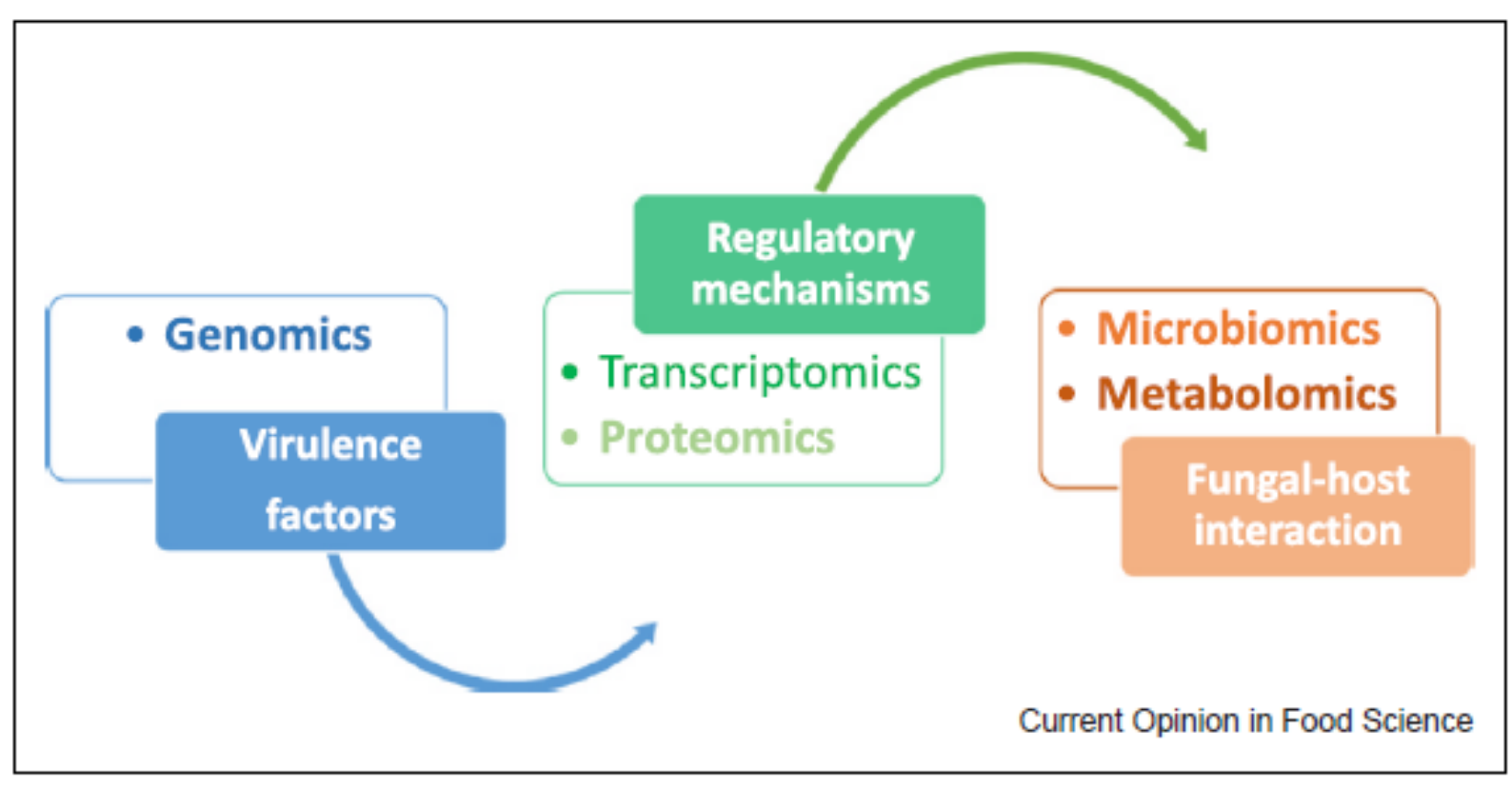
Yeasts also have a remarkable ability to produce bioactive volatiles.



New antifungals



Omic technologies



Thanks for attention

