Summa Phytopathologica

The Official Journal of São Paulo State Plant Pathology Association

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Escopo da *Summa Phytopathologica*

Summa Phytopathologica (SP) é um periódico direcionado para publicações de trabalhos de pesquisa, originais na área de fitopatologia, publicado trimestralmente, desde 1975.

SP é uma publicação oficial da Associação Paulista de Fitopatologia, (APF) que possui quase 500 associados de vários estados do Brasil e países da América Latina. Os trabalhos de pesquisadores não associados também são aceitos, uma vez que, respeite as normas de publicação, aspectos éticos, legislação vigente e normas da biossegurança.

A Comissão Editorial é composta por um presidente, um secretário e um tesoureiro, eleitos em assembléia dos membros associados da APF, e também um Conselho Editorial, composto por quatorze pesquisadores de diferentes instituições.

Os manuscritos podem ser submetidos em Português, Inglês e Espanhol, que são revisados por três assessores "ad-hoc", especialistas nas áreas (bacteriologia, micologia, virologia, nematologia, controle e manejo de doenças, ecologia, epidemiologia, etiologia, genética e resistência, pós-colheita, técnicas em fitopatologia, etc.), trabalhos de revisão também são aceitos para publicação. O padrão adotado para apresentação é o mesmo da ABNT (Associação Brasileira de Normas Técnicas) e regras internacionais ISO. As instruções completas para preparo e submissão dos manuscritos são publicados em todos os volumes nas páginas finais.

O periódico ***SP*** é indexado no AGRIS, CAB Abstracts, Review of Plant Pathology, Biological Abstracts, Scopus e SciELO Brazil. A forma abreviada para o nome do periódico é ***Summa Phytopathol.***

Scope of *Summa Phytopathologica*

Summa Phytopathologica (SP) is a peer-reviewed journal publishing original research articles focusing exclusively on all aspects of plant pathology. The scientific journal *Summa Phytopathologica* has been published quarterly since 1975.

SP is the official publication of the APF - *Associação Paulista de Fitopatologia* (São Paulo State Plant Pathology Association), which has approximately 500 members from Brazil, Latin America and other countries overseas. Membership annual fees solely support the journal but membership in the Society is not a prerequisite for publication in the journal. Page charges are higher for nonmembers.

Its editorial board is composed by a president, a secretary, and a treasurer (elected during APF business meeting), and an editorial committee formed by fourteen plant pathologists from the main Universities and research institutions of São Paulo State.

Manuscripts may be submitted for consideration of publication in Portuguese, Spanish or English languages. Submission implies nonsubmission elsewhere. The submitted manuscripts are reviewed by three *ad-hoc* assessors, which are plant pathology specialists designated by the editorial board. Subject areas of the research articles include both fundamental and applied plant pathology (bacteriology, disease control and pest management, ecology, epidemiology, etiology, genetics and resistance, mycology, nematology, postharvest diseases and techniques, and virology). In addition to research articles, reviews articles provide up-to-date summaries of recent advances in plant pathology. The standards adopted for manuscript preparation follow the local rules from ABNT (*Associação Brasileira de Normas Térnicas* – Brazilian Association for Technical Standards) and international rules from ISO. Complete instructions for manuscript preparation and submission are presented in the first issue of ***SP*** published every year.

The journal ***SP*** is currently indexed in AGRIS, CAB Abstracts, Review of Plant Pathology, Biological Abstracts, Scopus e SciELO Brazil.

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HOMENAGEM PÓSTUMA

Prof. Armando Bergamin Filho

(04/05/1948 – 31/01/2025)[1]

Armando Bergamin Filho iniciou sua carreira como docente no Departamento de Fitopatologia, atualmente Departamento de Fitopatologia e Nematologia, da ESALQ-USP, em 1974. Foi nessa instituição que recebeu os títulos de mestre e doutor em ciências, respectivamente em 1973 e 1975. Desde o início de sua jornada científica, realizou pesquisa em instituições internacionais, destacando-se a Osaka Prefectural University, no Japão, Pennsylvania State University, nos EUA, e INRA-Versailles, na França. Foi apresentado à epidemiologia de doenças de plantas durante sua estadia nos EUA entre 1977-1978. No entanto, foi com o apoio do Prof. Jurgen Kranz, da Universidade de Giessen, na Alemanha, que se firmou no cenário internacional, participando da maioria dos Workshops Internacionais sobre Epidemiologia de Doenças de Plantas e realizando pesquisas com financiamento de consórcios internacionais. Foi pioneiro no estudo epidemiológico de doenças de plantas no Brasil, área internacionalmente reconhecida, graças ao expressivo grupo de pesquisadores em atuação no País e também às colaborações de longa data com os Professores Bernhard Hau, Richard Berger, Tim Gottwald, Serge Savary e Laetitia Willocquet.

Publicou cerca de 140 trabalhos em periódicos científicos e orientou ao redor de 60 alunos de pós-graduação. Foi editor dos dois volumes do *Manual de Fitopatologia* em suas quatro últimas edições e autor do livro *Doenças de Plantas Tropicais: Epidemiologia e Controle Econômico*, obra elogiada pelo eminente Prof. J.C. Zadoks na seção de book review da European Journal of Plant Pathology.

Prof. Bergamin foi um dos fundadores do *Grupo Paulista de Fitopatologia*, presente na maioria dos Congressos organizados pelo Grupo e com atuação marcante, seja nas palestras que proferiu, seja na participação como debatedor ou moderador em seções científicas. Recebeu distinções diversas, como o Prêmio Paulista de Fitopatologia, do Grupo Paulista de Fitopatologia; os prêmios Destaque da Fitopatologia e Álvaro Santos Costa, da Sociedade Brasileira de Fitopatologia; além do título de Destaque em Ciência, do Governo do Estado de São Paulo e a nomeação como *Fellow da American Phytopathological Society*.

Aqueles que o conheceram e tiveram o privilégio de trabalhar com Armando Bergamin Filho se lembrarão de seu compromisso com a ciência de alta qualidade, de seus argumentos precisos apoiados na filosofia, de seu incentivo e apoio aos colegas, bem como de seu brilhante senso de humor. Muitos outros que não o conheceram pessoalmente se beneficiarão de sua contribuição científica divulgada em livros, periódicos científicos, publicações de extensão, vídeos de palestras e de aulas, dentre outros. Sua didática sempre foi destaque em sua carreira e fonte de inspiração a todos os seus alunos. Profundamente respeitado pelos alunos e colegas, Bergamin era também admirado por seu pensamento independente, suas análises precisas e sua generosidade de espírito. Deixa esposa, filhos, netos, muitas saudades e muitos amigos.

[1]Texto preparado e enviado por Lilian Amorim (ESALQ-USP)

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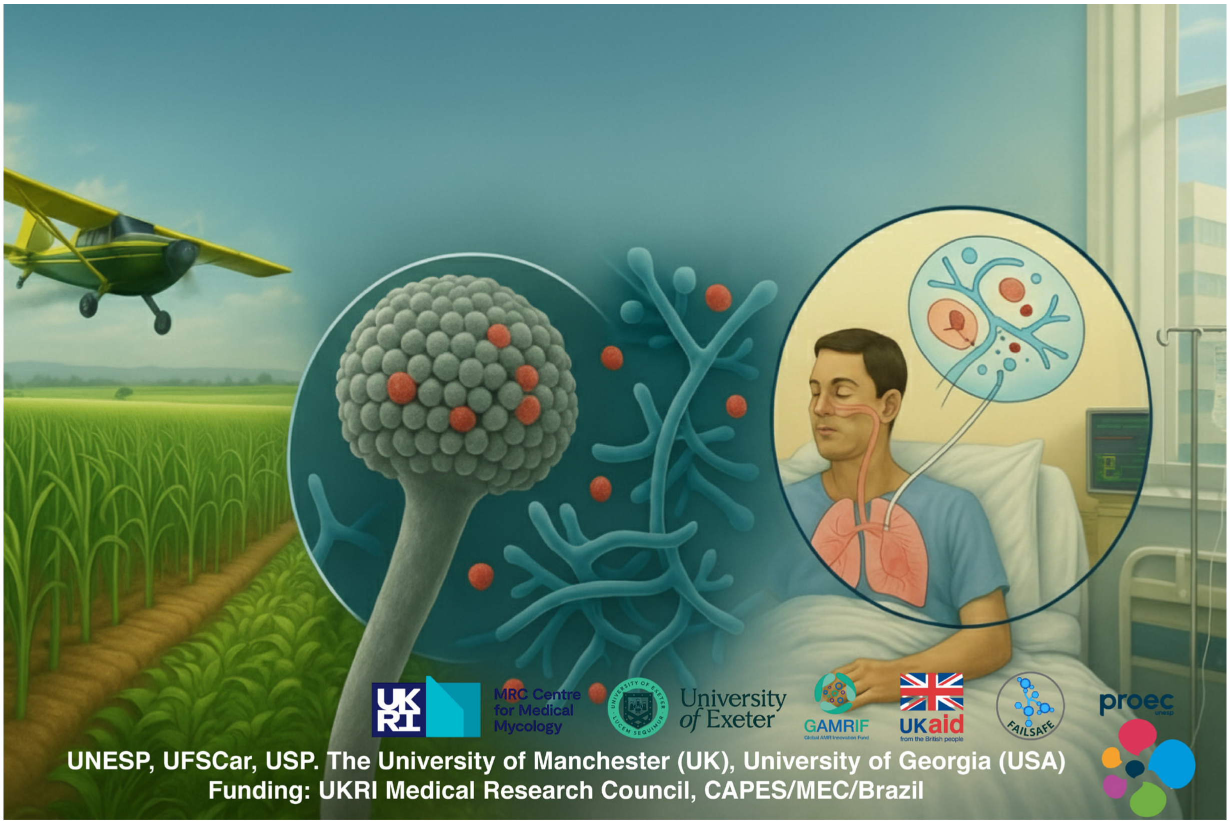
Proceedings



Brazilian Network Meeting on *Aspergillus fumigatus* Antimicrobial Resistance

Theme: Protecting Health in the Face of Agricultural Pressures

UNESP Botucatu | December 3–5, 2025

Summa Phytopathol.	Botucatu	v. 51	Special Supplement	December 2025

v. 51 *Special Supplement*, December. 2025

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SUMÁRIO

POSTERS

About the event

This scientific meeting will bring together researchers, healthcare professionals, industry representatives, and policymakers to address the growing challenge of antifungal resistance in *Aspergillus fumigatus*, with a focus on the impact of agricultural fungicide use.

The program includes clinical panels, technical sessions, thematic workgroups, policy roundtables with national and international authorities, and a global policy panel with representatives from FAO, CDC, Ministry of Agriculture and Livestock (MAPA), Ministry of Health, Anvisa, Fiocruz, State Secretariats of Health, Environment and Agriculture, Embrapa, UNESP, UFSCar, USP, Unicamp, The University of Manchester (UK), University of Georgia (USA), and many other organizations.

This meeting will foster focused, collaborative discussions and presentations, bringing together researchers, clinicians, industry representatives, and policymakers. The goal is to critically examine the bioecology of *Aspergillus fumigatus* and the escalating challenge of antimicrobial resistance, understanding the societal consequences of current policies and practices. We aim to identify gaps and develop actionable strategies that explicitly prioritize public health. Ultimately, this meeting seeks to inspire local Brazilian researchers and strengthen our collaborative network for impactful change.

The event will culminate in the development and signing of a **Public Motion for Health-First Fungicide Policies**, consolidating institutional commitments to public health and the One Health approach.

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Vice President
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Support from the UK Research and Innovation (UKRI)/ Medical Research Council FAILSAFE program (Fungal Antimicrobial Resistance Innovations for Low- and Middle-Income Countries) made this Meeting and its Proceedings possible. The program's foundational funding and collaboration enabled the multidisciplinary research across partner institutions in the United Kingdom (University of Manchester), the United States (University of Georgia), and Brazil (UNESP, UFSCar) that culminated in this scientific event. The personnel of UNESP's International Office (AREX) were instrumental in implementing the interinstitutional agreements. The Organizing Committee also gratefully acknowledges FUNDUNESP for its essential role in managing event logistics and financial expenditure implementation. This activity was part of University Extension Event 2025 /12595, approved by PROEC - the Pro-Rectory of University Extension and Culture at UNESP.

Speakers' Directory (Alphabetical order)

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Full Program

Brazilian Network Meeting on *Aspergillus fumigatus* Antimicrobial Resistance
Theme: *Protecting Health in the Face of Agricultural Pressures*
UNESP Botucatu | December 3–5, 2025

Day 1 - Wednesday, December 03, 2025

The AMR Crisis: Clinical Realities & Agricultural Drivers

Objective: Uncover the direct links between agricultural practices and the clinical burden of antifungal resistance.

08:30 – 09:00 | Registration & Welcome Coffee

09:00 – 10:00 | Institutional welcoming, Opening Remarks & Context Settings

- **Institutional welcoming**: **Patrícia Pintor dos Reis** (UNESP Host Representative) & **Renata Tigulini de Souza** (Health and Environment Surveillance Secretariat – SVSA, Brazilian Ministry of Health, representing all invited speakers sectors)
- **Opening Remarks:** *Confronting a public crisis and setting the stage for a Health-First future: Aligning science, policy, and agriculture to overcome antifungal resistance* – **Paulo Ceresini** (UNESP Ilha Solteira, Brazil), Presidency of the Meeting, on behalf of the Organizing Committee

Context Setting:

- **Keynote 1:** *Aspergillus fumigatus: The journey from environmental saprophyte to invasive human pathogen* **Gustavo H. Goldman** (University of São Paulo – USP / INCT Human Fungal Pathogens)
- **Keynote 2:** *The Legacy of the UK FAILSAFE Program – Why Fund Research into Fungal Antimicrobial Resistance?* **Michael Bromley** (The University of Manchester, UK)

10:00 – 11:15 | Plenary Clinical Panel: Azole-Resistant Aspergillosis – The Human Cost in Brazil & Europe

Moderator: Gabriel Gasparini Camargo (CGLAB / SVSA, Ministry of Health)

Speakers:

- **Angélica Zaninelli Schreiber** (UNICAMP Medical School) – *Critical treatment failures and diagnostic gaps for aspergillosis resistant to environmental fungicides*
- **Luciana Trilles** (Fiocruz) – *Surveillance of azole-resistant Aspergillus fumigatus in environment air samples from Latin America*
- **Ricardo de Souza Cavalcante** (UNESP Botucatu) – *Clinical cases and challenges in rural and urban areas of São Paulo*
- **Paul Verweij** (Radboud University Medical Center, Nijmegen, The Netherlands) – *Clinical cases from the Netherlands*
- **Rose-Anne Lavergne** (Nantes Université, France) – *Clinical cases of Aspergillus fumigatus in France and adopting a One Health approach*

11:15 – 11:30 | Coffee Break

11:30 – 13:15 | Plenary Session: The Agricultural Drivers – How Fungicides Drive Resistance

Moderators: Michelle Momany (University of Georgia, USA) & Waldir Cintra de Jesus Junior (UFSCar, Brazil)

Speakers:

- **Bart A. Fraaije** (Wageningen University & Research, The Netherlands) – *Mechanisms and evolution of triazole resistance in agricultural fields*
- **Eva Stukenbrock** (Christian-Albrechts University of Kiel, Germany – Online) – *The evolution of fungicide resistance is widespread in fungal communities associated with agricultural soils and crops*
- **Marin Brewer** (University of Georgia, USA) – *Sustainable agricultural practices for One Health: Responsible fungicide use, resistance mitigation, and alternative control strategies to reduce antifungal resistance*
- **Kelly Simões**, **Luis Demant**, **Andreas Goertz** (FRAC / FRAC-BR) – *The Fungicide Resistance Action Committee – Its purpose, scope and activities*
- **Martin Semar** (CropLife International AFR EG, BASF SE, Germany), Kevin Doughty (CLI AFR EG Consultant, Germany), Helge Sierotzki (CLI AFR EG Syngenta, Switzerland), Juergen Derpmann (CLI AFR EG Bayer AG CropScience Division, Germany) – *CropLife International Antifungal Resistance Expert Group's perspective on antifungal cross-resistance: The need for a One Health approach*
- **Paulo C. Ceresini** (UNESP Ilha Solteira, Brazil) – *The systemic failure of fungicide resistance management in the agroecosystem and its public health implications*

13:15 – 14:15 | Lunch

14:15 – 16:15 | Parallel Breakout Workgroups: Formulating Health-First Solutions

Technical guidance for the Meeting's Working Groups: A One Health framework for assessing fungicide essentiality.

Scientific Coordinator and Independent Facilitator for consensus: **Paulo C. Ceresin**i (UNESP, Brazil).

Workgroup A – Strengthening Clinical Surveillance & Reporting

Objective: To identify best practices and actionable strategies for improving clinical surveillance, reporting, and patient management for azole-resistant aspergillosis, linking it to environmental drivers.

Lead: Ricardo de Souza Cavalcante (UNESP Botucatu, Brazil).

Contributors: Angélica Zaninelli Schreiber (UNICAMP), **Florent Morio** (Nantes Université), **Gabriel Gasparini Camargo** (SVSA / Ministry of Health - MS), **Gideane Mendes de Oliveira** (SVSA / MS), **Paul Verweij** (Radboud UMC), **Rose-Anne Lavergne** (Nantes Université), **Ana Zaccaro** (F2G Ltd.), **Kevin Doughty** (CropLife International, AFR EG Consultant)

Workgroup B – Mechanisms of Resistance & Environmental Monitoring Guidelines

Objective: To define key mechanisms driving antifungal resistance and establish robust guidelines for environmental monitoring and surveillance of *A. fumigatus* and other resistant fungi.

Lead: Bart A. Fraaije (WUR)

Contributors: Daniel de Assis Bastos (UFMG), **Katherin Castro Rios** (UIS, Faculdad de Salud), **Michelle Mommany** (UGA), **Norman Van Rhijn** (University of Manchester), **Eveline Snelders** (WUR – Online), **Eva Stukenbrock** (CAUK – Online), **Endrews Delbaje** (USP), **Michael Bottery** (UoM), **Marin Brewer** (UGA), **Martin Semar** (BASF)

Workgroup C – Policy & Regulatory Strategies for Agricultural Fungicides

Objective: To evaluate current agricultural fungicide policies and propose health-first strategies, including restrictions on high-risk compounds to mitigate AMR.

Lead: Paulo C. Ceresini (UNESP)

Contributors: Gustavo Henrique Goldman (USP), **Jorge Pinto Ferreira** (FAO), **Maria Augusta Carvalho Rodrigues** (ANVISA), **Michael Bromley** (UoM), **Paulo Renato Matos Lopes** (UNESP), **Plínio Trabasso** (UNICAMP), **Cláudia Vieira Godoy**, **Janine Passos Lima & Maurício Conrado Meyer** (EMBRAPA), **Ana Cândido (**Regulatory Manager for Chemical Crop Protection Products, CropLife Brazil (CLB)), Panelist appointed by the Secretariat of Agricultural Defense, Ministry of Agriculture and Livestock (MAPA)

Workgroup D – Public Health Advocacy & Communication Strategy

Objective: To develop robust communication and advocacy strategies to promote a One Health approach to antifungal resistance, engaging stakeholders from government, research, and agriculture.

Lead: Luciana Trilles (Fiocruz)

Contributors: Clara Valero (University of Manchester), **Dallas Smith** (CDC, Atlanta, USA), **Rafael Wesley Bastos** (UFRN), **Renata Tigulini de Souza** (MS), **Juliana do Amaral Moreira Conforti Vaz** (MAPA), **Danilo Tancler Stipp** (UFSCar), **Maria Thereza Bonilha Dubugras** (Institute of Health – SES-SP), **Hélia Maria Piedade** (SEMIL-SP), **Raquel Lozano Guilharducci** (SEMIL-SP), **Martha Regina Lucizano Garcia** (CATI / SAA-SP), **Juergen Derpmann** (CropLife International - CLI, AFR EG).

16:15 – 16:45 | Coffee Break

16:45 – 17:45 | Working Group Findings: Gaps and Needs for "Health-First Fungicide Policies": Each working group reports back on its key findings, highlighting the major challenges, actionable pathways, and priority areas for advancing Health-First Fungicide Policies.

17:45 – 18:00 | Short Break

18:00 – 18:30 | Keynote Lecture

Speaker: Daniel de Assis Santos (UFMG, Brazil)

Title: *From the field to the clinic: agrochemical fungicides promote enzymatic inactivation of clinical antifungal.*

18:30 – 20:00 | Shared Interests Forum & Evening Poster Session

Facilitator: Michelle Momany (University of Georgia, USA)

Format: Networking and collaboration exchange on *A. fumigatus* AMR.

20:15 – 22:15 | Dinner and Break

22:15 | End of Day 1

Day 2 - Thursday, December 04, 2025

Science & Policy for a Health-Driven Change

Objective: Identify and leverage scientific tools and policy mechanisms to contain antifungal resistance, explicitly prioritizing health outcomes.

07:30 – 08:00 | Welcome Coffee & Poster Session

08:00 – 10:15 | Session Block 1A: Tracking Resistance Dissemination and One Health Monitoring

Moderator: Michael Bottery (The University of Manchester, UK)

Speakers:

- **Eveline Snelders** (Wageningen University & Research, The Netherlands – Online) *Global dissemination patterns of resistant Aspergillus fumigatus and comparative genomics of resistant strains*
- **Michelle Momany,** J. Stanislaw, A. Mahmud, O. Nemeth, & **Marin Brewer** (University of Georgia, USA) ***Aspergillus fumigatus*** *isolates from agricultural field sites where the fungicide ipflufenoquin was applied are less sensitive to DHODH inhibitors*
- **Paulo C. Ceresini, Tatiane C. Silva, Lucas Lopes e Silva, Paulo Renato Matos Lopes** & many collaborators (UNESP Dracena, Ilha Solteira and Jaboticabal campi, UFSCar Buri, Brazil) *Environmental dynamics of* ***Aspergillus fumigatus*** *in Brazilian agroecosystems: Climatic drivers of airborne and soilborne populations*
- **Norman van Rhijn** (The University of Manchester, UK) *Climate change impacts on fungal pathogens*
- **Paulo C. Ceresini, Tatiane C. Silva, Lucas Lopes e Silva,** & many collaborators (UNESP Dracena, Ilha Solteira and Jaboticabal campi, UFSCar Buri, Brazil) *Widespread azole resistance and co-resistance to a clinical DHODH inhibitor in* ***Aspergillus fumigatus*** *from fungicide-intensive Brazilian agroecosystems*

10:15 – 11:15 | Session Block 1B: Lessons Learned on Tracking Antifungal Resistance Spread from Other Pathosystems under the One Health Perspective

Speakers:

- **Rafael Wesley Bastos** (UFRN, Brazil) *The Candida auris case: Antifungal Resistance in yeast from a One Health Perspective*
- **Florent Morio** (Nantes Université, France) *The Candida parapsilosis case: Antifungal Resistance under One Health*
- **Danilo Tancler Stipp** (UFSCar, Brazil) *Antifungal resistance in livestock animals: a silent threat to One Health*

11:15 – 11:45 | Coffee Break & Poster Session

11:45 – 13:00 | Session Block 2: Policy Levers and Legal Action for Accountability

Moderator: Gustavo H. Goldman (University of São Paulo – USP, Brazil)

Speakers:

- **Maria Augusta Carvalho Rodrigues** (ANVISA – Brazilian Health Regulatory Agency) *Pesticide registration and reevaluation in Brazil: Legal framework and regulatory actions for fungicides*
- His Excellency **Gabriel Infante Magalhães Martins [Public Prosecutor's Office (Ministério Público Federal)]** *Environmental damage caused by pesticides and path to legal accountability against antifungal resistance*
- **Renata Tigulini de Souza** (CGLAB / SVSA – Brazilian Ministry of Health) *Integrating antifungal resistance into Brazil's National One Health Action Plan against Antimicrobial Resistance (PAN-BR One Health)*
- **Paul Verweij** (Radboud University Medical Center, Nijmegen, The Netherlands) *EU policies on antifungal management*
- **Ana Luiza Zaccaro** (F2G Ltd., UK) *The pace of prevention: regulatory hurdles and the challenge of developing clinical antifungals to keep pace with environmental-driven resistance*
- **Arthur Gomes** [Chemical Crop Protection Director, CropLife Brazil (CLB)] *Regulatory and R&D Challenges in Crop Protection*: *A Brazilian perspective on timelines, uncertainty, and the need for a more innovation-friendly regulatory framework.*

13:00 – 14:00 | Lunch

14:00 – 15:30 | Round Table: "Realigning Agricultural Policy to Prioritize Public Health" – Tackling Domestic Challenges for One Health

Moderators: Paulo Cezar Ceresini (UNESP, Brazil) & Waldir Cintra de Jesus Junior (UFSCar, Brazil)

Panelists:

- **Plínio Trabasso** (UNICAMP, Brazil) *Clinical-epidemiological profile of patients with invasive aspergillosis in public hospitals in Campinas, Brazil in the last decade*
- **Painelist appointed by MAPA** (Ministry of Agriculture and Livestock, Brazil) *Regulatory synergy: aligning agriculture's defense with public health for sustainable agribusiness*
  Claudia Vieira Godoy & **Maurício Conrado Meyer** (EMBRAPA, Brazil) *Resistance-driven policy: lessons from a major plant pathogen for managing Aspergillus fumigatus*
- **Luciana Trilles** (Fiocruz, Brazil) *The critical role of environmental antifungal resistance monitoring in shaping evidence-based health policies*
- **Michael Bottery** (The University of Manchester, UK) *The Honest Broker: The role of independent science in shaping sustainable agriculture for public health*
- **Arthur Gomes [Chemical Crop Protection Director, CropLife Brazil (CLB)]** *Discussing the effectiveness and limitations of voluntary industry action versus regulatory measures*

15:30 – 16:00 | Coffee Break & Poster Session

16:00 – 17:30 | International Panel: "One Health & Fungal AMR – Global and Local Agencies' Perspectives on Public Policy and Surveillance"

Moderator: Michael Bromley (The University of Manchester, UK)

Panelists:

- **Jorge Pinto Ferreira** (Food and Agriculture Organization – FAO, Italy) *The FAO's role in addressing antimicrobial resistance in agrifoodsystems*
- **Dallas Smith** (Centers for Disease Control and Prevention – CDC, USA) *Azole-resistant **Aspergillus fumigatus**: Surveillance gaps and U.S. Centers for Disease Control and Prevention initiative*
- **Gideane Mendes de Oliveira** & **Renata Tigulini de Souza** (SVSA / Brazilian Ministry of Health) *The Brazilian Ministry of Health perspective on One Health and antifungal resistance*
- **Maria Augusta Carvalho Rodrigues** (ANVISA, Brazil *The National Health Surveillance Agency's perspective on risk management for antifungal resistance*
- **Janine Passos Lima** *(EMBRAPA, Brazil) Public policies for the rational use of fungicides and combating antimicrobial resistance*
- **Painelist appointed by MAPA** (Ministry of Agriculture and Livestock, Brazil) *Agricultural defense's role in cross-ministry AMR control efforts*

17:30 – 18:00 | Short Break

18:00 – 18:30 | Keynote Lecture

Speaker: Katherin Castro-Ríos (Universidad Industrial de Santander, Colombia)

Title: *Aspergillus fumigatus in the food production chain and azole resistance*

18:30 – 20:00 | Early Career Researchers (ECR) Forum on Aspergillus fumigatus Antimicrobial Resistance

Facilitators: Clara Valero (The University of Manchester, UK) & **Rafael Wesley Bastos** (UFRN, Brazil)

Format: Reflections on challenges and opportunities, networking, and collaboration.

20:15 – 22:15 | Dinner and Break
22:15 | End of Day 2

Day 3 - Friday, December 05, 2025
Action and Accountability

08:00 – 08:30 | Welcome Coffee & Poster Session

08:30 – 9:30 | Working Groups – Finalizing the "Public Motion for Health-First Fungicide Policies"

Objective: Consolidate the contributions from all thematic workgroups (A–D) into a unified, consensus-ready draft of the *Public Motion for Health-First Fungicide Policies*. Each group will finalize revisions, address cross-cutting recommendations, and harmonize terminology to ensure scientific coherence and policy neutrality.

Facilitators: Ricardo de Souza Cavalcante (UNESP Botucatu), **Bart A. Fraaije** (WUR), **Paulo C. Ceresini** (UNESP Ilha Solteira), and **Luciana Trilles** (Fiocruz)

9:30 – 10:00 | Coffee Break & Poster Session

10:00 – 10:30 | Consensus & Submission Session – Public Motion for Health-First Fungicide Policies

Moderators: Paulo C. Ceresini (UNESP, Brazil) & **Waldir de Jesus Jr.** (UFSCar)

Objective: Review, discretionary endorsement, and approval of the final text of the *Public Motion for Health-First Fungicide Policies,* followed by live submission to *One Health* with all voluntary co-authors present.

Note: This session will be open to all cross-sector meeting participants to ensure inclusive discussion and authorship confirmation.

Process: 1. Presentation of the final consolidated text developed from Workgroups A–D. 2.Open discussion for final amendments and endorsements. 3. Electronic co-authorship confirmation and live submission to the journal *One Health.*

10:30 – 10:45| Concluding Remarks: *From Consensus to Consequence: The road ahead for Health-First policies*
Paulo Ceresini (UNESP, Brazil), Presidency of the Meeting, on behalf of the Organizing Committee

10:45 – 11:00 | Brief Press Conference (Integrated): "Brazil's Fight Against Antimicrobial Resistance"

Cross-sector collaboration toward the One Health agenda. Voluntary short statements from sector representatives, summarizing shared consensus and future actions. Media coordination by Fundunesp Communication & UNESP's Communications and Press Office (CLI) and *Jornal da UNESP.*

11:00 – 11:15 | Transition & Closing Logistics

Distribution of certificates and brief closing announcements by the Organizing Committee.

11:30 – 13:00 | Farewell Lunch

Venue: Restaurant Chácara Floresta – Botucatu, SP

Host: Fundunesp & Organizing Committee

Informal farewell gathering celebrating the successful consensus and the launch of the Brazilian Network for Fungal AMR Surveillance.

13:00 | Meeting Adjourns

ABSTRACTS

Brazilian Network Meeting: *Aspergillus fumigatus* Antifungal Resistance – Protecting Health in the Face of Agricultural Pressures

PRESIDENTIAL ABSTRACT, ON BEHALF OF THE MEETING ORGANIZING COMMITTEE / Resumo Presidencial, em nome da Comissão Organizadora do evento.

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ABSTRACT: The Brazilian Network Meeting on *Aspergillus fumigatus* Antimicrobial Resistance (UNESP Botucatu, 3–5 December 2025) was convened to confront a rapidly escalating public health emergency posed by environmentally selected antifungal-resistant pathogens—a challenge that directly links agricultural practices to clinical treatment failures, demanding a coordinated One Health response. Over three days, the scientific contributions presented across medicine, agriculture, microbiology, epidemiology, fungal genomics, and regulatory science collectively demonstrated how fragmented sectoral actions have contributed to a systemic failure in managing antifungal resistance.

The meeting established an unequivocal chain of evidence. Clinical data revealed persistently high mortality from invasive aspergillosis in Brazil and internationally, with treatment failures increasingly associated with infections caused by environmentally driven azole-resistant *A. fumigatus*. Environmental and molecular surveillance studies confirmed widespread resistance to agricultural azoles across Latin America, together with emerging cross-resistance and co-resistance mechanisms that threaten both current and next-generation antifungal drugs. The crisis extends beyond *Aspergillus*. Complementary studies broadened this perspective by documenting similar risks in other opportunistic fungi—such as *Candida auris* and *C. parapsilosis*—showing that agricultural selection pressures pose a wider One Health hazard spanning environmental, clinical, veterinary, and food-chain interfaces.

Regulatory and public health contributions underscored the importance of coordinated multisectoral governance. The Ministry of Health (MS) demonstrated robust engagement through national initiatives in diagnostics, surveillance, and stewardship; Embrapa researchers emphasized sustainable agricultural practices and innovation in biological control; state health secretariats contributed essential epidemiological perspectives and education and social communication actions in One Health; and ANVISA provided critical insight into the regulatory complexity of antifungal drug development and approval. Importantly, the Federal Prosecution Service of Brazil (Ministério Público Federal – MPF) has advanced a critical legal perspective by addressing environmental damage caused by pesticides and the pathways toward legal accountability. These contributions highlight that several public institutions in Brazil, within their respective mandates, are actively responding to the crisis of antifungal resistance affecting public health. Together, they reinforce the need for coordinated, cross-sectoral action.

The meeting also documented the formal absence of one ministry with regulatory responsibility. Participation was initially confirmed, later excused due to unforeseen circumstances, and ultimately declined—through official channels—on the grounds that antifungal resistance was outside the ministry's institutional scope. This contrasts with the ministry's own publicly established programs for managing fungicide resistance within the sector. Despite a subsequent formal appeal reiterating the scientific and institutional relevance of its involvement, no representative had been confirmed by the time these Proceedings were finalized. The Organizing Committee remained fully prepared to receive a designated representative at any time, and the corresponding seats in the scientific program were deliberately kept open in anticipation of a possible confirmation. This is noted solely to document the timeline of intersectoral engagement in an area where multisectoral alignment is fundamental to One Health governance.

In response to the evidence assembled, the meeting adopted a forward-looking strategy to transform scientific findings into coordinated action. A consensus-based Public Motion for Health-First Fungicide Policies will be collaboratively prepared by Workgroups A–D and voluntarily endorsed during the closing plenary, followed by live submission to the journal *One Health*. Voluntary endorsement will be open to participants acting in an independent scientific, professional, or civil capacity, without institutional mandate or conflict of interest that may compromise the Motion's public-interest orientation. This process ensures that the final document reflects evidence-based priorities and safeguards its integrity as a public health–driven initiative. This Motion intends to provide a concrete framework for realigning agricultural policy with public health imperatives, including mandatory cross-resistance risk assessments, support for low-AMR-risk alternatives, and the integration of public health criteria into fungicide registration and regulation. In parallel, participants will contribute to a comprehensive Review Article to be submitted to *Frontiers in Fungal Biology*. These outcomes ensure an inclusive, evidence-driven, and non-coercive pathway for multisectoral collaboration while preserving full editorial neutrality.

Taken together, the scientific contributions presented in these Proceedings demonstrate an urgent need for agricultural decision-making and regulatory practices to explicitly integrate public health protection. Antifungal resistance is no longer solely a clinical concern; it is an environmental, agricultural, and societal challenge requiring coordinated One Health policy. This meeting has therefore moved from documenting the magnitude of the threat to outlining a feasible solution through the collective capacity of Brazilian and international institutions. The path forward is codified in the Public Motion. The challenge now is to overcome the institutional inertia that prevents its adoption.

Keywords: One Health; antifungal resistance; agricultural fungicides; *Aspergillus fumigatus*; public policy; environmental resistance.

Palavras-chave: Uma Só Saúde; resistência antifúngica; fungicidas agrícolas; *Aspergillus fumigatus*; políticas públicas; resistência ambiental.

ACKNOWLEDGMENTS

The Meeting and these Proceedings were made possible through the support of the **UKRI/MRC FAILSAFE – Fungal AMR Innovations for LMICs** program, whose funding enabled multidisciplinary research across partner institutions in the United Kingdom (University of Manchester), the United States (University of Georgia), and Brazil (UNESP, UFSCar, USP), as well as the full realization of this scientific event. The Organizing Committee expresses deep gratitude to the **Editorial Office of *Summa Phytopathologica*** for opening its pages to the publication of the Extended Abstracts, and to all members of the Committee – especially the early-career researchers and students—whose dedication, scientific rigor, and collaborative effort made this Meeting and its outcomes possible.

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ASPERGILLUS FUMIGATUS: THE JOURNEY FROM ENVIRONMENTAL SAPROPHYTE TO INVASIVE HUMAN PATHOGEN / *Aspergillus fumigatus*: A jornada de saprófita ambiental a patógeno humano invasivo.

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ABSTRACT: *Aspergillus fumigatus* is a ubiquitous filamentous fungus, playing a critical role as a saprophyte in global carbon and nitrogen recycling by decomposing organic matter (1). Despite its environmental prevalence, it has emerged as the primary etiological agent of invasive aspergillosis (IA), a life-threatening infection with mortality rates often exceeding 50% in immunocompromised populations. This presentation will delineate the multifaceted journey of *A. fumigatus* from an environmental bystander to a formidable human pathogen, focusing on the triad of fungal virulence factors, host immune vulnerabilities, and the growing challenge of antifungal resistance. The transition begins with the efficient dispersal of conidia, which are small enough (2–3 µm) to reach the pulmonary alveoli. A critical first step in pathogenesis is the evasion of the innate immune system. The conidial surface, decorated with hydrophobic rodlets and melanin, provides resistance to phagocytosis and oxidative burst by alveolar macrophages (2). Upon germination, the switch to hyphal growth is a pivotal turning point. The elongating hyphae, essential for tissue invasion, are targeted by the neutrophil-mediated immune response. To survive this assault, *A. fumigatus* employs a formidable arsenal of virulence attributes, including the secretion of hydrolases (e.g., proteases and phospholipases) that facilitate nutrient acquisition and tissue penetration, the production of toxins like gliotoxin that induce immune cell apoptosis, and efficient nutrient acquisition systems for iron and other essential micronutrients within the hostile host environment (2). The fungus does not act alone; its pathogenicity is context-dependent, requiring a susceptible host. The primary risk factor for IA is profound neutropenia, followed by impaired neutrophil function (e.g., in chronic granulomatous disease or corticosteroid therapy), and solid organ or stem cell transplantation. The breakdown of physical barriers, such as from prior lung disease or viral infection, further facilitates invasion. This host-pathogen interaction is increasingly complicated by the alarming global rise of triazole-resistant *A. fumigatus* isolates. Resistance, primarily linked to mutations in the *cyp51A* gene, can arise from agricultural azole use, applying a selective environmental pressure that pre-exposes the fungus before it even enters a clinical setting, rendering frontline prophylaxis and therapy ineffective (3). In conclusion, the pathogenesis of *A. fumigatus* is not mediated by a single "toxin" but is a complex, multifactorial process. It is a testament to evolutionary adaptation, where traits selected for survival in a competitive soil environment coincidentally confer the ability to colonize and invade a human host with a breached immune defense (1-3). Understanding this intricate journey—from conidial inhalation to angioinvasive disease, set against the backdrop of rising antifungal resistance—is paramount for developing novel diagnostic tools, antifungal strategies, and effective immune-modulatory therapies to improve patient outcomes.

Keywords: virulence factors; host-pathogen interaction; immune evasion; triazole resistance; pathogenesis.

Palavras-chave: fatores de virulência; interação hospedeiro-patógeno; evasão imune; resistência a triazóis; patogênese.

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WHY FUND RESEARCH INTO FUNGAL ANTIMICROBIAL RESISTANCE? / Por que financiar pesquisas sobre resistência fúngica a antimicrobianos?

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ABSTRACT: In 2022 the WHO published the Fungal Priority Pathogens List (1) which describes the key etiological agents responsible for over 2 million deaths each year. This document represents the first global effort to systematically prioritise fungal pathogens based on unmet research and development needs and perceived public health importance. The reports stated aim was to focus and drive further research and policy interventions thereby strengthening the global response to fungal infections and antifungal resistance. This was followed by additional WHO reports on the state of clinical diagnostics and drug discovery for fungal infection. Together these highlight the dearth of antifungals in the development pipeline, deficiencies in diagnosing fungal disease and the expansion of antifungal resistance in the critical fungal pathogens *Candia auris* and notably *Aspergillus fumigatus*. Over the past 30 years groups in the Netherlands, Manchester, London, Georgia and other centres across the globe have been describing a seemingly inexorable expansion of triazole resistant *A. fumigatus* populations in the environment, likely driven by the extensive contamination of the environment with azole fungicides. Armed with this evidence, in 2025, a report instigated by the European Commission and led by the European Food Standards Agency laid out the issues with azole use in agriculture and horticulture, their impact in reducing the effectiveness of clinical antifungals and presenting a future outlook (2). In this talk I will summarise key risks to sustainability of current antifungal and those in development.

Keywords: research funding; fungal priority pathogens list; drug pipeline; diagnostics; environmental contamination.

Palavras-chave: financiamento de pesquisa; lista de patógenos fúngicos prioritários; pipeline de drogas; diagnósticos; contaminação ambiental.

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CRITICAL TREATMENT FAILURES AND DIAGNOSTIC GAPS FOR ASPERGILLOSIS RESISTANT TO ENVIRONMENTAL FUNGICIDES / Falhas críticas de tratamento e lacunas diagnósticas para aspergilose resistente a fungicidas ambientais.

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ABSTRACT: *Aspergillus fumigatus* is an opportunistic pathogen associated with high mortality rates, for which azole antifungals represent first-line therapy. The UNICAMP Clinical Hospital (HC-UNICAMP), a medium- to high-complexity tertiary center, is located in a region surrounded by intensive agricultural activity, where land preparation, planting, and harvesting occur continuously. The institution provides care for patients from the Campinas Metropolitan Region, as well as additional cities from neighboring states, totaling 42 municipalities. As a regional reference center, HC-UNICAMP treats a high number of high-risk patients, including transplant recipients, immunocompromised individuals, and approximately 250 patients followed at its cystic fibrosis clinic. Upon joining UNICAMP, limitations in laboratory resources and methodologies for in-depth fungal studies prompted the establishment of the Fungal Research Laboratory (LIF-FCM-UNICAMP) culture collection around 1998. In the early 2000s, azole-resistant *A. fumigatus*, typically associated with *CYP51A* mutations, was first reported. Given that HC-UNICAMP serves numerous high-risk patients, the detection of *CYP51A*-mutant isolates among our clinical samples in 2019 (2) reinforced the necessity for continuous surveillance. Accordingly, prospective monitoring of azole resistance was initiated, despite the constraints of a public teaching hospital setting. Between 2018 and 2021, in an observational, prospective surveillance study of inpatients with invasive aspergillosis in our hospital, high mortality was observed in individuals over the age of 21, giving them a lower survival rate than younger patients (1). The preservation of fungi in the collection has also enabled important retrospective studies (7, 3). An *A. fumigatus* isolate from the hospital environment, harboring a resistance mutation only described in 2024, was found to have been maintained in the collection since 1998 (4). Sequential patient isolates further allowed the assessment of diverse fungal behaviors, influenced by underlying diseases, accuracy of presumptive diagnoses (clinical and biomarker-based), empirical treatments, confirmation of susceptibility, adjustments following detection of resistance, "in vitro" antifungal agents combination tests and evaluation of novel antifungal compounds. Over 25 years of studying *A. fumigatus*, more than 1,500 isolates have undergone antifungal susceptibility testing according to CLSI and/or EUCAST/BRCast standards. Isolates exhibiting high minimum inhibitory concentrations, classified as azole-resistant, were analyzed for mutations in the *CYP51A* gene. Resistant isolates lacking *CYP51A* alterations were further screened for mutations in *hmg1* gene, and microsatellite genotyping was performed to assess genetic relationships among sequential isolates from the same patient, between different patients and trying to access environmental sources (5). Our findings range from highly azole-resistant isolates with no currently identified genetic determinants (7) to isolates recovered from patients receiving prolonged azole therapy, showing resistance mutations considered of clinical origin (6). The majority of mutations detected in clinical isolates correspond to so-called environmental mutations, which may have been acquired in the hospital surroundings, within the facility, or carried by the patient as initial colonizers. Unfortunately, for the treatment of invasive fungal infections, therapeutic options are still extremely limited. The ongoing challenge is to systematically detect, report, and manage invasive *A. fumigatus* infections, while elucidating the specific role of each resistance type in colonization, disease progression, and therapeutic outcomes.

Keywords: clinical surveillance; culture collection; *CYP51A* mutations; hospital environment; treatment failure.

Palavras-chave: vigilância clínica; coleção de culturas; mutações *CYP51A*; ambiente hospitalar; falha terapêutica.

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SURVEILLANCE OF AZOLE-RESISTANT *ASPERGILLUS FUMIGATUS* IN ENVIRONMENT AIR SAMPLES FROM LATIN AMERICA / Vigilância de *Aspergillus fumigatus* resistente a azóis em amostras de ar ambiental da América Latina.

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ABSTRACT: The emergence and spread of multidrug-resistant pathogenic fungi pose a growing threat to public health and global food security (1). *Aspergillus fumigatus* can cause a wide range of infections in both immunocompromised and immunocompetent individuals, from allergic syndromes to invasive aspergillosis (IA). When the fungal spores are inhaled, a lung infection can be established, with an estimated global incidence exceeding 300,000 cases annually, but it is probably an underestimation of the real picture. In most cases, the immune system in the respiratory tract efficiently prevents the development of disease. However, when it fails, IA becomes a life-threatening disease very difficult to manage (2). Limited accuracy in diagnosis or treatment strategy derives increased mortality rates varying from 50% to 100%. Triazoles are the first-choice for the treatment of aspergillosis, but in the last two decades a growing number of both clinical and environmental isolates have exhibited azole resistance. Prolonged and repeated fungal exposure to azoles creates selective pressure, favoring the survival and proliferation of resistant fungal strains within a population and the extensive agricultural application of azole fungicides seems to be a major driver of environmental resistance, increasingly reflected in clinical cases (3). Although environmental hotspots harboring resistant *A. fumigatus* have been identified, the true extent of general human exposure to these strains remains largely unknown. Therefore, the present work investigated the resistance to azoles of *A. fumigatus* collected from the air of 11 countries in Latin America. A total of 9,077 air samples were analyzed, resulting in the isolation of 2,152 *A. fumigatus* strains which were tested against itraconazole, voriconazole, isavuconazole, and

posaconazole. Resistant/non-wildtype strains underwent mutation identification of the *CYP51A* gene and the detection of genotypes of the resistant strains by short tandem repeats (STR). Resistant/non-wildtype strains were identified in 58 strains (2.7%), being that 11 of them were resistant to more than one azole type (multidrug-resistant). The highest number of resistances was identified against isavuconazole (N=35), mainly in Costa Rica, Brazil and Guatemala. The same countries are the only ones which report the use of mefentrifluconazole, a new azole fungicide for several crops, with broad spectrum of action, likewise isavuconazole. There was no correlation between resistance and *CYP51A* mutation, as well as resistance and genotypes. Considering that 86.5% of the samples were collected in urban areas and 13.5% in rural areas, we can only suggest that the use of azole fungicides might potentially induce resistance in environmental *A. fumigatus* populations, which may result in limiting treatment options even more. Additionally, the predominance of urban samples indicates that resistant strains are likely already circulating among patients.

Keywords: air sampling; Latin America; environmental surveillance; *CYP51A*; mefentrifluconazole.

Palavras-chave: amostragem de ar; América Latina; vigilância ambiental; *CYP51A*; mefentrifluconazol.

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CLINICAL CASES AND CHALLENGES IN RURAL AND URBAN AREAS OF SÃO PAULO / Casos clínicos e desafios em áreas rurais e urbanas de São Paulo.

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ABSTRACT: *Aspergillus* spp. is a genus responsible for life-threatening invasive fungal infections in humans. In immunosuppressed hosts such as patients with hematologic malignancies, organ transplant recipients, and individuals undergoing corticosteroid therapy—whose prevalence is increasing in the population—invasive aspergillosis (IA) is observed. Patients with residual pulmonary lesions are susceptible to developing chronic pulmonary aspergillosis (CPA), which, in countries like Brazil, has a high prevalence due to its association with tuberculosis. Resistance to azoles, the main class of antifungal drugs used to treat aspergillosis, is a limiting factor in the clinical management of patients with aspergillosis, including both IA and CPA. This resistance may arise from prior antifungal use by the patient. However, in recent decades, resistance has been shown to be acquired in the environment, particularly related to the use of azoles in agriculture. IA is an acute disease that progresses rapidly to death if not properly treated. Studies have shown that IA caused by *Aspergillus* spp. strains that are non–wild type for voriconazole is associated with higher mortality, likely due to antifungal treatment failure (1, 2). In these non–wild type strains for voriconazole, TR34/L98H and TR46/Y121F/T289A mutations have been detected in the *cyp51A* gene, characteristic of environmentally acquired resistance (1). Although less studied, azole resistance can also be harmful to patients with CPA. Effective disease control in these patients depends on long courses of azole therapy, and resistance may negatively affect their survival. In Brazil, there are limited data on *Aspergillus* spp. resistance to azoles, particularly regarding its origin. Nevertheless, this issue raises great concern, as agriculture is a major economic activity in which azole fungicides are used, creating potential for the development of resistance. *In vitro* studies have shown that fungicides used in agriculture increase the minimum inhibitory concentrations (MICs) of azoles in *Aspergillus* spp (3). Evaluation of clinical and environmental strains from the interior of the state of São Paulo, Brazil, shows that, overall, azoles exhibit MIC values above the epidemiological cutoff, although they remain susceptible to voriconazole and itraconazole (4). However, cases of patients with IA and CPA showing poor response to azole therapy have been observed. Molecular studies aimed at determining the origin of resistance—through sequencing of the *cyp51A* gene and efflux pump–encoding genes—have been conducted in the interior of São Paulo to better understand the resistance profile of *Aspergillus*, particularly from the Fumigati and Flavi sections, and its impact on patients' clinical outcomes.

Keywords: invasive aspergillosis; chronic pulmonary aspergillosis; *cyp51A* mutations; treatment failure; São Paulo.

Palavras-chave: aspergilose invasiva; aspergilose pulmonar crônica; mutações *cyp51A*; falha terapêutica; São Paulo.

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CLINICAL CASES OF *ASPERGILLUS FUMIGATUS* IN FRANCE AND ADOPTING A ONE HEALTH APPROACH / Casos clínicos de *Aspergillus fumigatus* na França e a adoção de uma abordagem de Saúde Única.

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ABSTRACT: Invasive aspergillosis are the third invasive fungal infections reported in France according to the French National Center of Invasive Mycosis and Antifungals (NRCMA) (1, 2). The first-line treatment of invasive aspergillosis are triazole antifungal drugs (3) however the overall rate of azole-resistance is currently estimated at 8.1% for isolates from invasive infections (4). Since the first clinical case of azole-resistant *Aspergillus fumigatus* (AR*Af*) in France in 1997 following long-term itraconazole treatment (5), several studies have been conducted to understand the epidemiology of AR*Af*, in the context of emerging azole resistance linked to tandem repetition in *CYP51A* gene promoter in early 2010's. While azole resistance prevalence was initially low in patients treated for haematological malignancies (6), clinical cases have reported invasive aspergillosis due to TR_{34}/L98H or TR_{46}/Y121F/T289A isolates (7, 8). Given the environmental origin of these two alterations, environmental surveys have confirmed the presence of resistant isolates in the environment close to patients (homes, fields) (7, 8). Other studies focused on patients with chronic pulmonary aspergillosis, particularly those with cystic fibrosis (CF) in whom the prevalence of azole resistance appeared to be higher (9, 10, 11, 12), with up to 17.9% of itraconazole resistance (12). Although not the only mutation observed, the environmental TR_{34}/L98H alteration was frequent in azole-resistant isolates. These data have prompted environmental studies to investigate possible hotspots of azole resistance. Outside hospital, numerous AR*Af* were found in market gardens, sawmills and flower planters (13, 14, 15) whereas resistant isolates were less frequently isolated from soil samples taken from fields (15, 16). Regarding

the hospital environment, whereas a study reported no environment azole-resistant isolates during major hospital demolition works (17), in another hospital, TR_{34}/L98H AR*Af* isolates were evidenced mainly from pots of tulips imported from the Netherlands (18). Several projects are currently pursuing these investigations using a One Health approach. Participative sciences involving students from French Schools of pharmacy (Urbazole project, France) or involving citizens (SporeWatchFrance project) are ongoing to assess the prevalence and distribution of AR*Af* in France. The French Aspergillus One-health project aims to identify hotspots as possible sources for selection of AR*Af* in the environment. This presentation will focus on our experience with clinical cases due to azole-resistant isolates and French studies in the One Heath context.

Keywords: environmental hotspots; clinical cases; cystic fibrosis; participatory surveillance; France.

Palavras-chave: hotspots ambientais; casos clínicos; fibrose cística; vigilância participativa; França.

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MECHANISMS AND EVOLUTION OF TRIAZOLE RESISTANCE IN AGRICULTURAL FIELDS / Mecanismos e evolução da resistência a triazóis em campos agrícolas.

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ABSTRACT: The fungus *Aspergillus fumigatus* is a mold commonly found on plant debris and in soil (1). It is also an opportunistic human pathogen causing a broad spectrum of diseases, ranging from allergic symptoms to life-threatening invasive infections (5). The incidence of invasive aspergillosis (IA) has been increasing in recent years largely due to increased numbers of immunocompromised individuals in the population (including patients with severe influenza and Covid-19) unable to fight off infection (5). Treatment of IA is difficult as there are few effective antifungal drugs without toxic side-effects. Triazoles are among the most widely used fungicides due to their efficacy and low toxicity. However, resistance to triazoles has evolved in clinical *A. fumigatus* isolates and is becoming more common, with serious consequences for the treatment of invasive infections (1, 2, 3). The first cases of azole resistance were reported in clinical isolates from the USA during the late 1980s. Recent studies have shown that resistance to medical azoles has increased in Europe. Azoles inhibit the enzyme sterol 14α-demethylase (CYP51), a key step in the synthesis of sterols essential for the integrity of cell membranes. Many different resistant strains, mostly with changes (mutations) that alter the CYP51 target protein have been isolated from patients undergoing azole therapy. Other resistance mechanisms remain unknown or have been elucidated, including increased expression of the *CYP51* gene, so that more of the target enzyme is produced, and overexpression of genes encoding proteins in the cell membrane that pump fungicides out of the cell (efflux pumps). Efflux pump overexpression can occur together with target-site based resistance mechanisms, contributing to a higher overall level of azole insensitivity (4). Since 2000, resistant *A. fumigatus* isolates have been found in the Netherlands in patients that have not received any azole treatment indicating an environment-to-person transmission route (1, 2). These isolates initially all belonged to a particular genotype group, having a *CYP51A* mutation resulting in the substitution of leucine by histidine at codon 98 (L98H) of the protein together with a 34-bp long DNA insert (tandem repeat (TR)) in the regulatory (promoter) sequence (TR34) leading to increased gene expression (1). Closely related fungal strains with TR34/L98H and TR46/Y121F/T289A are now frequently found worldwide in both the clinic and the wider environment since 1998 and 2008, respectively (1). New variants with additional mutations (e.g. TR34/L98H/T289A/I364V/G448S, TR46/Y121F/M172I/T289A/G448S and TR46/Y121F/T289A/S363P/I364V/G448S) are still evolving, and many of the TR34 and TR46 harboring strains are highly resistant to different azoles (triazoles and imidazoles) and to fungicides belonging to different classes, including methyl benzimidazoles (MBCs), quinone outside inhibitors (QoIs) and succinate dehydrogenase inhibitors (SDHIs) (1), commonly used to prevent fungal diseases in animals, birds and plants, and/or to preserve materials (e.g. wood, paints and fabrics). Detailed information on the origin and further spread of fungicide resistant strains of *A. fumigatus* in agricultural fields and the wider environment is therefore urgently needed (1, 2). This will enable thorough assessment of the extent of risk for fungicide resistance development at different hotspots, and strategies to slow down and/or prevent future spread of azole resistance may be implemented.

Keywords: *CYP51A* mutations; TR34/L98H; TR46/Y121F/T289A; efflux pumps; environmental transmission.

Palavras-chave: Mutações *CYP51A*; TR34/L98H; TR46/Y121F/T289A; bombas de efluxo; transmissão ambiental.

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THE EVOLUTION OF FUNGICIDE RESISTANCE IS WIDESPREAD IN FUNGAL COMMUNITIES ASSOCIATED WITH AGRICULTURAL SOILS AND CROPS / A evolução da resistência a fungicidas é generalizada em comunidades fúngicas associadas a solos agrícolas e culturas.

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ABSTRACT: Fungal pathogens can cause devastating diseases in cereal crops. For decades, agricultural fields have been treated with fungicides to reduce the impact of these diseases. However, the occurrence of fungicide-resistant pathogens has dramatically increased in recent years (1). Plants are colonised by diverse communities of fungi, and we hypothesise that endophytic fungi may also evolve resistance to fungicides through recurrent exposure to these compounds. Our first objective was to characterise the diversity of endophytic fungi associated with wheat in agricultural fields. By taking samples from plots treated and not treated with fungicides, we demonstrate that fungicide treatments significantly reduce the diversity of non-pathogenic endophytic fungi. We experimentally validated this finding in a greenhouse experiment using agricultural soil as a substrate and a microbial inoculum. Wheat seedlings were sprayed with the fungicide fluconazole at concentrations comparable to those used in agricultural fields. As was observed in the field, this treatment drastically reduced fungal diversity; however, some fungi persisted in the fungicide-treated wheat seedlings. To investigate Fluconazole tolerance further, we isolated endophytic and epiphytic fungi from wheat leaves. These mycobiomes included a wide variety of Ascomycete species, including *Penicillium* and *Aspergillus* species. We conducted an *in vitro* test to assess tolerance to the fungicide and demonstrated that several wheat-associated fungi are able to tolerate high levels of fluconazole. We speculate that decades of exposure to fungicides in the field have resulted in communities of fungicide-resistant fungi. Our findings have implications for human health, as agricultural environments may serve as reservoirs for new opportunistic human pathogens that have acquired antifungal resistance.

Keywords: fungicide resistance; endophytic fungi; mycobiome; agriculture; fluconazole.

Palavras-chave: resistência a fungicidas; fungos endofíticos; micobioma; agricultura; fluconazol.

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SUSTAINABLE AGRICULTURAL PRACTICES FOR ONE HEALTH: RESPONSIBLE FUNGICIDE USE, RESISTANCE MITIGATION, AND ALTERNATIVE CONTROL STRATEGIES TO REDUCE ANTIFUNGAL RESISTANCE / Práticas agrícolas sustentáveis para uma saúde: uso responsável de fungicidas, mitigação da resistência e estratégias alternativas de controle para reduzir a resistência antifúngica.

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ABSTRACT: Fungal diseases threaten global agricultural productivity and human health, driving the widespread use of fungicides as a primary control measure. While effective and economical, extensive fungicide application, particularly single-site fungicides, has accelerated the emergence and spread of resistant fungal populations in both environmental and clinical settings (3). This issue is especially critical for the environmentally acquired, plant-associated pathogen *Aspergillus fumigatus*, where agricultural azole use has contributed to the development of pan-azole-resistant strains that are difficult to treat in clinical settings. Moreover, many environmental and clinical strains exhibit multi-fungicide resistance, indicating that reducing azole use alone may not be sufficient to address the problem, as these other widely used fungicides can continue to select for azole-resistant populations of *A. fumigatus* (1, 4). Addressing this One Health challenge requires integrated, sustainable strategies that will be discussed in this presentation, including responsible fungicide use, resistance mitigation, and adoption of alternative control strategies (6). Responsible fungicide use involves reducing prophylactic applications, rotating modes of action, and applying treatments based on disease forecasting (2). Effective resistance mitigation requires ongoing environmental surveillance, genomic tracking of resistance mutations, stakeholder engagement to raise awareness of risks of antifungal resistance development in human pathogens in agricultural settings, and coordinated efforts to limit dual agricultural–clinical antifungal use. Alternative low-risk practices, such as integrated pest management (IPM), cultural methods, biological control, improved waste and compost management, and precision technologies to reduce fungicide inputs while maintaining disease control. Strengthening plant resistance through breeding and genetic approaches offers a long-term solution by decreasing dependency on chemical controls (5). Together, these strategies reduce selection pressure, limit the spread of resistant strains, and protect the efficacy of existing antifungal compounds. By integrating chemical, biological, cultural, and genetic approaches within a One Health framework, we can promote sustainable disease management, safeguard food security and food safety, and preserve antifungal effectiveness for both agriculture and human medicine.

Keywords: sustainable agriculture; resistance mitigation; integrated pest management; precision agriculture; stakeholder engagement.

Palavras-chave: agricultura sustentável; mitigação da resistência; manejo integrado de pragas; agricultura de precisão; engajamento das partes interessadas.

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THE FUNGICIDE RESISTANCE ACTION COMMITTEE – ITS PURPOSE, SCOPE AND ACTIVITIES / O Comitê de Ação à Resistência a Fungicidas – Seu Propósito, Escopo e Atividades.

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ABSTRACT: Fungicides are an important component of integrated crop protection strategies in agriculture and thus are essential to global food security. The Fungicide Resistance Action Committee (FRAC) (1) is a Specialist Technical Group under the umbrella of CropLife International (CLI). As an inter-company committee, it is dedicated to facilitating the safeguarding of the long-term effectiveness of fungicides by promoting sustainable fungicide use practices and resistance management strategies in agriculture around the globe. FRAC's mission is to unite global and local expertise to provide science-based guidance for fungicide resistance strategies to facilitate the maintenance of effective disease management in agriculture by: a) equipping farmers and advisors with practical tools and expert knowledge to help the implementation of effective strategies for resistance management, b) providing guidance to policymakers on sustainable crop protection through science-led fungicide resistance monitoring and strategies, c) linking research and agricultural practice to improve the effectiveness and adoption of fungicide resistance management strategies. FRAC is structured with a Global Steering Committee that sets strategy and oversees global coordination. Specialized Working Groups and Expert Fora focus on specific fungicide modes of action (MoAs) or crops, while Regional and National Committees (e.g. FRAC Brazil) adapt strategies to local needs. Technical experts and researchers support this work through data analysis, field monitoring, and scientific assessments. FRAC's expertise and knowledge in areas such as fungicidal MoAs, cross-resistance, sensitivity status and resistance management recommendations for key MoAs, monitoring methodology or the resistance risk for plant pathogens are publicly accessible (www.frac.info). For years, technical experts from FRAC have been closely linked to CLI's Antifungal Resistance Expert Group. They collaborate with researchers around the globe across OneHealth disciplines on the topic of dual use of fungicidal/antifungal compounds. Despite the fact that human fungal pathogens present in the environment (e.g. *Aspergillus fumigatus*), are not targets of fungicide applications for crop protection, FRAC's broad experience in understanding and managing resistance when applying fungicides to control fungal pathogens in agricultural environments can be of benefit in addressing the OneHealth challenge of dual antifungal use.

Keywords: Fungicide Resistance Action Committee; resistance management; modes of action; integrated pest management; knowledge transfer.

Palavras-chave: Comitê de Ação à Resistência a Fungicidas; manejo da resistência; modos de ação; manejo integrado de pragas; transferência de conhecimento.

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CROPLIFE INTERNATIONAL ANTIFUNGAL RESISTANCE EXPERT GROUP´S PERSPECTIVE ON ANTIFUNGAL CROSS-RESISTANCE: THE NEED FOR A ONE HEALTH APPROACH / Perspectiva do Grupo de Especialistas em Resistência Antifúngica da CropLife International sobre a resistência cruzada a antifúngicos: A necessidade de uma Abordagem de Saúde Única.

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ABSTRACT: CropLife International recognizes the importance of antifungal resistance (AFR) development in human pathogens, and the potential link to the use of agricultural fungicides, and biocides. For more than a decade, CropLife International has been contributing to the build-up of knowledge on the potential contribution of agricultural fungicide use to AFR emergence, for example by commissioning and publishing review papers on this subject (1, 2, 3). Here, particular emphasis has been placed on the definition and identification of hotspots for *Aspergillus fumigatus* (agricultural settings that support the selection, amplification and spread of azole-resistant genotypes – e.g. organic waste piles) and coldspots (settings that do not provide such conditions, e.g. broadacre crops) (4). In addition, we have funded projects by independent research organizations to validate the hotspot / coldspot concept (5). We have also commissioned a survey, taking the Netherlands as an example, to identify plant waste routes in current practice for selected crops in order to "map" potential hotspots for *A. fumigatus* resistance emergence and identify possible mitigation measures. Finally, we exchange with regulatory authorities and policymakers and network actively within "coalitions of the willing" to identify measures to reduce the risk that fungicides contribute to the emergence of resistance of *A. fumigatus* towards existing and new antifungals used in hospitals. Given the need for fungicides to support food security and food safety, we advocate for a "One Health" approach to the issue that considers the societal need for antifungals and fungicides for medical, agricultural and biocidal purposes. CLI stresses the need for new fungicidal modes of action to be made available for agriculture in order to maintain the crop protection toolbox and thus the ability of farmers to achieve the necessary level of productivity. Beyond the preservation of crop yield, resistance management is a major element of crop protection practice, and this depends on the availability of a diversity of modes of action per crop, including new ones that are complementary to existing modes of action, which are, to a greater or lesser extent, undergoing attrition as the result of the emergence of resistance within target pathogen populations. Given that the convergence of development pipelines in the agricultural and pharmaceutical domains is likely to continue, a risk-based approach to assessing future fungicidal modes of action is appropriate within this "One-Health" context. CropLife International companies will continue to work together with farmers' associations, the medical profession, governments, research institutes and other involved industries to address resistance development in human pathogens, particularly *A. fumigatus*, and to translate scientific findings into effective mitigation measures.

Keywords: CropLife International; hotspots; coldspots; risk mitigation; fungicide development.

Palavras-chave: CropLife International; hotspots; coldspots; mitigação de risco; desenvolvimento de fungicidas.

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THE SYSTEMIC FAILURE OF FUNGICIDE RESISTANCE MANAGEMENT IN THE AGROECOSYSTEM AND ITS PUBLIC HEALTH IMPLICATIONS / A falha sistêmica do manejo da resistência a fungicidas no agroecossistema e suas implicações para a saúde pública.

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ABSTRACT: The rapid emergence of azole-resistant *Aspergillus fumigatus*, including environmentally selected multi-azole resistant genotypes, represents an escalating public health crisis directly linked to agricultural fungicide use. This trend marks a stark departure from historical patterns of clinical azole susceptibility in Brazil and South America (9, 10). By integrating three key datasets—Brazilian fungicide sales (2000–2023) (13, 5), a comprehensive analysis of registered fungicide formulations on the Brazilian market (8), and a national survey of fungicide resistance in plant pathogens (2)—this study demonstrates that the scale, velocity, and complexity of fungicide use in Brazil have created an inevitable environmental selection system that bridges the evolution of resistance in plant and human pathogens. Over two decades, a nine-fold increase in total fungicide sales has transformed croplands into a pervasive resistance reservoir (5). This pressure was accelerated by the explosive growth of high-risk, single-site fungicide classes, such as strobilurins (CAGR 62.7%). By 2023, the overlapping use of multiple fungicide classes selected for broad-spectrum multidrug resistance (MDR), with mechanistic MDR confirmed in major plant pathogens (16, 14, 12) and mirroring non-*cyp51A* resistance mechanisms in *A. fumigatus* (4, 3). Environmental and clinical surveillance in Brazil corroborates this threat, revealing a progressive increase in azole MICs and the emergence of resistant strains carrying novel *cyp51A* mutations—including TR34/L98H/S297T/F495I and TR46/F495I—in both clinical and hospital environmental samples (11, 7). This is further supported by environmental monitoring that has detected resistant *A. fumigatus* in agricultural settings such as sugarcane plantations (3) and in air samples across Latin America (15).

The implementation of anti-resistance strategies for plant pathogens has collapsed, hampered by a lack of nationwide disease forecasting surveillance and a technical literacy gap among growers (2). Consequently, farmers are often left with no alternative to calendar-based, preventive spraying. Regulatory failure is starkly evidenced by the fact that 60.8% of formulations are solo-active, high-risk products, while 73.7% of mixtures combine two single-site modes of action. The national survey documented multi-class resistance in at least 18 major fungal pathogens (2), signaling the agronomic collapse of single-site fungicides and confirming a mechanistic convergence with clinical resistance in *A. fumigatus*. Addressing this crisis demands a One Health–integrated policy that mandates the co-formulation of high-risk fungicides with multisite partners—particularly for new active ingredients with dual-use potential in agriculture and medicine, such as DHODH inhibitors (6)—alongside nationwide resistance surveillance and mandatory cross-resistance risk assessments for registration. Complementarily, the rapid market expansion of multisite, low-AMR-risk microbial biofungicides offers a viable path to reduce environmental selection pressure.

Keywords: Azole resistance, One Health, multidrug resistance (MDR), environmental selection, regulatory failure, biofungicides.

Palavras-chave: Resistência a triazóis, Saúde Única, resistência multidroga (RMD), seleção ambiental, falha regulatória, biofungicidas.

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DECIPHERING NON-*CYP51A* MEDIATED AZOLE RESISTANCE IN *Aspergillus fumigatus* / Decifrando a resistência a azóis não mediada por *Cyp51A* em *Aspergillus fumigatus*.

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ABSTRACT: Invasive fungal infections represent a significant threat to public health, particularly for immunocompromised individuals. The fungus *Aspergillus fumigatus* is a ubiquitous opportunistic pathogen and the primary agent of Invasive Pulmonary Aspergillosis. Azole antifungals are the main treatment for these infections. However, the increasing prevalence of strains resistant to these drugs has become a global health crisis. While mutations in the *cyp51A* gene, the azole targeted gene, are a well-established and frequently investigated resistance mechanism, our research focuses on a critical challenge: resistance mechanisms not mediated by *cyp51A*. These alternative pathways, involving complex genetic and regulatory networks, are less understood and represent a significant gap in our knowledge, with implications for clinical management and public health (1, 2, 3). The intensive use of azole fungicides in agriculture is a key selective pressure driving the emergence and spread of resistant strains in the environment (4). These resistant environmental isolates can subsequently cause infections in humans that are untreatable from the outset, decoupling resistance from clinical antifungal use and creating a public health problem directly linked to agricultural practices. Our contribution to the manifesto aims to elucidate the genetic basis of these alternative resistance mechanisms. Using an integrated genomic and functional approach, we investigate a collection of azole-resistant clinical and environmental *A. fumigatus* isolates that lack the well-known mutations in the *cyp51A* gene. Through whole-genome sequencing, genome-wide association studies (GWAS), and transcriptomic analyses, we seek to identify novel genetic variants and molecular pathways associated with resistance. Preliminary results already indicate the existence of a diversity of *cyp51A*-independent resistant isolates, validating the relevance of this investigation. By unraveling the genetic complexity behind emerging resistance, our work provides robust scientific evidence to inform health policies that promote the sustainable use of fungicides, thereby protecting the efficacy of antifungals that are critical for human medicine.

Keywords: alternative resistance mechanisms; genomics; transcriptomics; environmental selection; public policy.

Palavras-chave: mecanismos alternativos de resistência; genômica; transcriptômica; seleção ambiental; política pública.

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PROESA: INTERINSTITUTIONAL STRATEGIES FOR ONE HEALTH EDUCATION IN THE FACE OF FUNGAL RESISTANCE CHALLENGES / Proesa: Estratégias interinstitucionais para a educação em Saúde Única frente aos desafios da resistência fúngica.

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ABSTRACT: The National Program for Sanitary Education in Agricultural Defense (Proesa) was established on May 15, 2008, through Normative Instruction No. 28 (1), and is part of the Unified System for Agricultural Health Attention (Suasa) (2). Its general objective is to promote, through educational actions, animal health, plant health, and the safety and quality of Brazilian agricultural products and their derivatives (IN 28/2008). Proesa fosters interinstitutional articulation to implement public policies for sanitary education benefiting One Health and socio-environmental sustainability. To reestablish the national management of the Program, the Sanitary Education Sector (Seduc) was created in October 2022, linked to the structure of the Secretariat of Agricultural Defense (SDA) of the Ministry of Agriculture and Livestock (Mapa). Since then, innovative strategies focused on promoting sanitary education within the scope of Proesa have been developed. Among these strategies, the implementation of a participatory governance structure, involving Suasa members, and others, through the creation of the Proesa Collaborative National Network, and the prioritization of learner-centered educational actions, as opposed to approaches limited to simple information transmission or leafleting, stand out. The intersectorality promoted by the Program allows different institutions—public, private, and from civil society—to act in a coordinated manner, expanding the reach and effectiveness of the actions. The Proesa Network serves as a channel for the exchange of experiences and knowledge, in addition to acting as a mobilizing, fostering, and executing body for sanitary education projects in various regions of Brazil. It also serves an advisory and consulting function for the Program's management. Through the Network, educational projects and plans are realized, articulated by structures such as the Regional Sanitary Education Centers, State Commissions for Sanitary Education, and thematic Technical Groups. Among the formed Technical Groups, the Pesticides Working Group (*GT Agrotóxicos*) stands out, aiming to establish a National Plan for Sanitary Education on Pesticides, with guidelines, goals, and indicators to guide Suasa members regarding educational strategies aimed at mitigating serious problems related to pesticide use, such as indiscriminate use, the trade of illegal products, and microbial resistance. The proposal is to consolidate, through the Proesa Network, a broad One Health education network focused on the theme of pesticides. Also noteworthy are the methodological guidelines developed by Proesa, with an emphasis on the Sanitary Education Caravans—social mobilization actions whose main objectives are the training of multipliers and the carrying out of educational activities in rural and urban communities, reaching diverse target audiences. The Caravans have five structuring characteristics: interinstitutionality and interdisciplinarity, mass communication, use of participatory methodologies, training of multipliers, and evaluation. The presentation will explore concrete experiences from the Caravans, which have already raised awareness among more than 14,000 people about the prevention of health risks, including the conscious use of agricultural products and the impacts of these inputs on collective health. Through the Caravans, Proesa has worked at the interface between public health, agricultural production, and the environment, promoting educational actions that value the dialogue between scientific and popular knowledge, always focusing on the learner. The presentation aims to demonstrate how interinstitutional mobilization and participatory education can contribute to strengthening the Brazilian response to the challenges of fungal resistance, promoting health protection from an integrated and systemic perspective.

Keywords: health education; plant protection; interinstitutional collaboration; pesticides; public policy.

Palavras-chave: educação sanitária; defesa fitossanitária; colaboração interinstitucional; agrotóxicos; política pública.

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STATE PLAN FOR EDUCATION AND SOCIAL COMMUNICATION IN ONE HEALTH / Plano Estadual de Educação e Comunicação Social em Saúde Única.

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ABSTRACT: On August 17, 2022, the Technical Commission for the development and management of the State Plan for Education and Social Communication in One Health was established through Decree 67.052 (1), to integrate the Secretariats of Agriculture and Supply, Environment, Infrastructure and Logistics, and Health of the State of São Paulo. The initiative aims to develop and implement programs, conduct investigations, and build public policies and legal frameworks where various sectors communicate and collaborate to achieve better outcomes, aligned with the principles and objectives of One Health. The technical commission is responsible for establishing guidelines, proposing methodologies, and evaluating the results of education and social communication actions in One Health, promoting good agricultural practices, animal welfare, and the preservation of the environment and human health (2). Educational actions that promote discussions and the dissemination of knowledge, training collaborative professionals, are essential, as only knowledge can lead to changes in individual and collective habits and behaviors (3). The Plan aims to promote the integration of the Secretariats through a communication flow, enhance the epidemiological surveillance of diseases, develop mechanisms for seeking sustainable sociocultural strategies, and engage stakeholders to play their role as subjects of the required actions, developing and implementing health education actions based on the principles of One Health (4). The target audience of the Plan includes professionals in the fields of health, agriculture, and the environment, the general public according to the involved actors and socio-epidemiological scenarios that comprise the health issues of interest in One Health, the press, and representatives of the agribusiness production chain. Theme proposals to be evaluated by the commission may be representative of the needs or priorities of the proposing secretariat, as well as of a health emergency declared by an official body. The definition of the priority theme, for the actions to be carried out, due to an identified health risk or at the suggestion of commission members, will be jointly assessed by representatives of the three secretariats. At least one specific plan shall be developed and executed per year, with others possible according to the priorities of the involved secretariats, jointly defined by the commission. The specific plans will be monitored, according to the execution periodicity, by the commission members, with an evaluation of these actions, making the necessary adjustments to promote the effectiveness of the proposed results. An annual report of the executed activities will also be prepared and published.

Keywords: health education; social communication; interinstitutional commission; public policy; São Paulo.

Palavras-chave: educação em saúde; comunicação social; comissão interinstitucional; política pública; São Paulo.

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FROM THE FIELD TO THE CLINIC: AGROCHEMICAL FUNGICIDES PROMOTE ENZYMATIC INACTIVATION OF CLINICAL ANTIFUNGALS / Do campo ao hospital: fungicidas agrícolas promovem a inativação enzimática de antifúngicos clínicos.

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ABSTRACT: Cryptococcosis is a life-threatening disease caused by environmental fungi of the *Cryptococcus* genus. It disproportionately affects immunocompromised individuals, particularly people living with HIV/AIDS.

Globally, it accounts for approximately 19% of AIDS-related deaths, making it a significant public health concern (1). In Brazil, the mortality rate varies considerably depending on the region studied, with some areas reporting figures that exceed the global average. This elevated mortality is often linked to delayed diagnosis and treatment, as well as the increasing problem of antifungal resistance. One of the primary drugs used in both the induction and maintenance phases of cryptococcosis treatment is fluconazole, a triazole antifungal. However, fluconazole resistance is becoming increasingly prevalent and is considered a major factor contributing to poor treatment outcomes. This resistance can emerge during prolonged treatment or alternatively, patients can be infected with *Cryptococcus* strains that are already resistant, having acquired resistance mechanisms in the environment before infecting a human host. A growing body of evidence points to the role of agricultural fungicides in this environmental emergence of antifungal resistance. In our study, we evaluated the impact of several fungicidal agrochemicals from different chemical classes—including azoles, strobilurins, and fungal replication inhibitors—on the development of resistance in *Cryptococcus* strains. Our results revealed that exposure to these agrochemicals induced the overexpression of efflux pumps, which play a crucial role in reducing intracellular drug concentrations and thereby contributing to resistance. Additionally, in some strains exposed to azole fungicides, we observed upregulation of the *ERG11* gene, which encodes the target enzyme of fluconazole, 14-alpha-demethylase. Interestingly, despite the increased expression, no mutations were detected in the *ERG11* gene itself, suggesting that resistance was due to regulatory, rather than structural changes (2). To assess whether this *in vitro* resistance translated into *in vivo* consequences, we infected mice with the resistant strains. The results demonstrated that the resistance phenotype was maintained *in vivo*, underscoring the clinical relevance of environmentally induced resistance. In a subsequent phase of our research, we observed that fungicide exposure also triggered the expression of enzymes commonly associated with bacterial resistance to antibiotics. This led us to investigate further and ultimately discover a novel mechanism by which environmental fungi such as *Cryptococcus*, *Candida albicans*, and *Candida auris* modify fluconazole. After contact with agrochemicals, these fungi were found to chemically altering fluconazole. This structural modification increased the molecular size of the drug, causing steric hindrance that prevented effective binding to 14-alpha-demethylase, rendering the antifungal inactive. In conclusion, our findings demonstrate that the use of agricultural fungicides can induce cross-resistance to clinical antifungals in pathogenic yeasts. This resistance arises through complex mechanisms that involve metabolic and enzymatic pathways, some of which were previously thought to be limited to gene expression regulation. These insights highlight the urgent need to reassess the environmental use of antifungal agents and their broader implications for human health, particularly in regions with high burdens of opportunistic fungal infections.

Keywords: cryptococcosis; fluconazole resistance; agricultural fungicides; enzymatic inactivation; One Health.

Palavras-chave: criptococose; resistência ao fluconazol; fungicidas agrícolas; inativação enzimática; Saúde Única.

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GLOBAL DISSEMINATION PATTERNS OF RESISTANT *ASPERGILLUS FUMIGATUS* AND COMPARATIVE GENOMICS OF RESISTANT STRAINS / Padrões de disseminação global de *Aspergillus fumigatus* resistente e genômica comparativa de linhagens resistentes.

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ABSTRACT: Invasive aspergillosis, caused by *Aspergillus fumigatus*, represents a major global health threat, particularly due to rising resistance to triazole antifungals. Resistance is frequently associated with TR34/TR46 *cyp51A* haplotypes, detected in both environmental settings and in clinical isolates. While agricultural fungicide use is considered an important driver of resistance, the extent to which environmental hotspots contribute to human exposure remains poorly understood. *A. fumigatus* isolates collected in Dutch environmental hotspots and clinical centers, identified several cases of near-identical genomes in both sources, but could not explain the link between environmental and patient infections and possible exposure. Comparative analysis with more than 1,200 globally sourced genomes revealed extensive dissemination of certain resistant clonal groups across geographically distant regions, complicating the utility of genomics alone for source tracing (1). Complementary citizen science–based air sampling (>60,000 colonies) across the Netherlands revealed that approximately 4% of airborne isolates were resistant to clinical triazoles. Spatial modeling linked resistance to specific types of agricultural land use, while haplotyping indicated land-use–associated niche differentiation between dominant resistance haplotypes. Together, these findings highlight the global spread and ecological complexity of antifungal resistance in *A. fumigatus*. They demonstrate that resistance emerges from multifactorial selection pressures, both fungicide selection and niche differentiation, and that genomic data alone cannot explain environmental spread and exposure (1). This work underscores the urgency of multidisciplinary, One Health approaches integrating genomics, environmental surveillance, and geo information data to understand the growing public health threat posed by resistant *A. fumigatus*.

Keywords: genomic epidemiology; clonal dissemination; citizen science; environmental niche; One Health.

Palavras-chave: epidemiologia genômica; disseminação clonal; ciência cidadã; nicho ambiental; Saúde Única.

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ASPERGILLUS FUMIGATUS ISOLATES FROM AGRICULTURAL FIELD SITES WHERE THE FUNGICIDE IPFLUFENOQUIN WAS APPLIED ARE LESS SENSITIVE TO DHODH INHIBITORS / Isolados de *Aspergillus fumigatus* de campos agrícolas onde o fungicida ipflufenoquin foi aplicado são menos sensíveis a inibidores de DHODH.

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ABSTRACT: Fungi are important pathogens of plants and people. Few effective treatments exist against fungal pathogens and resistance is a growing problem. The filamentous fungus *Aspergillus fumigatus* is a ubiquitous saprophyte found in soil and leaf litter. It is also a devastating pathogen that is estimated to kill 1.8 million people annually (1). Previous work from our labs has shown that *A. fumigatus* resistant to azole fungicides, azole antifungal drugs, and other classes of fungicides used exclusively on crop plants is widespread in the USA (2). Recently a new class of chemicals targeting dihydroorotate dehydrogenase (DHODH) has been developed as both an agricultural fungicide (ipflufenoquin) and an antifungal drug (olorofim) (3, 4). Laboratory studies have shown that exposing *A. fumigatus*

to the fungicide ipflufenoquin causes mutations that also lead to resistance to the drug olorofim (5), but the effect of ipflufenoquin exposure in an agricultural setting has not been reported. In the current work we isolated *A. fumigatus* from agricultural field sites in Georgia (in the Southern USA) where ipflufenoquin was applied to apple trees approximately every 1-2 weeks, April - July of 2024 and 2025. We collected soil from the sites before the first ipflufenoquin application and soil and air samples multiple times during application. We isolated 198 *A. fumigatus* strains from soil samples before and during application and from air samples during application. We tested *A. fumigatus* isolates for minimal inhibitory concentrations (MICs) of ipflufenoquin and olorofim. We found that pre-application levels of sensitivity to both fungicide and drug were low. We also found that *A. fumigatus* isolates' sensitivity to ipflufenoquin fungicide and/or olorofim antifungal drug decreased in successive samples as the number of ipflufenoquin treatments increased. Our results suggest that agricultural use of DHODH inhibitor fungicides in agricultural settings can drive decreased efficacy of DHODH inhibitor antifungal drugs in clinical settings and underscore the need for thoughtful deployment of dual use agents.

Keywords: DHODH inhibitors; Ipflufenoquin; Olorofim; agricultural selection; dual use agents.

Palavras-chave: inibidores de DHODH; Ipflufenoquin; Olorofim; seleção agrícola; agentes de duplo uso.

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ENVIRONMENTAL DYNAMICS OF *Aspergillus fumigatus* IN BRAZILIAN AGROECOSYSTEMS: CLIMATIC DRIVERS OF AIRBORNE AND SOILBORNE POPULATIONS / Dinâmica ambiental de *Aspergillus fumigatus* em agroecossistemas Brasileiros: Fatores climáticos que influenciam populações fúngicas aéreas e do solo.

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ABSTRACT: The filamentous fungus *Aspergillus fumigatus* is a globally distributed saprobe and opportunistic pathogen increasingly recognized as a One Health sentinel for environmental antifungal resistance. However, its ecological dynamics in tropical agroecosystems remain poorly understood. This study—conducted within the FAILSAFE program (Fungal AMR Innovations for Low- and Middle-Income Countries; https://cmm-failsafe.com)—integrated aerobiological and soil monitoring with climatological analyses across four experimental sites in São Paulo State, Brazil (Dracena, Jaboticabal, Pereira Barreto, and Três Fronteiras) from December 2024 to October 2025. At each site, *A. fumigatus* was sampled monthly from air and soil. Airborne spores were collected using passive delta traps equipped with adhesive seals exposed for 30 days, overlaid with DRBC agar (Dichloran–Rose Bengal–Chloramphenicol + streptomycin), and incubated at 48 °C for 36–48 h. Soil (0–10 cm) samples were homogenized (0.2 g in 15 mL 0.1 M sodium pyrophosphate, vortexed intermittently for 30 min), plated (300 µL per dish), and incubated under identical conditions. Colonies morphologically consistent with *A. fumigatus* were enumerated and subcultured for azole sensitivity testing [reported in Ceresini et al. (1)].

Meteorological variables (temperature, relative humidity, solar radiation, rainfall, and irrigation) were retrieved from automatic weather stations, aggregated into monthly means, and normalized as z-scores. Two composite climatic indices were defined: Fungal Favorability Index (FFI = zTemp + zRH + zWater − zRad) and Climatic Stress Index (CSI = zRad + zTemp − zRH − zWater), where "Water" comprised rainfall plus 50 mm month^{-1} of supplemental irrigation at Três Fronteiras during the dry season. Airborne conidia loads (colonies per seal) and soil CFU g^{-1} (five replicates per site × month) were log-transformed [$\log_{10}(x + 1)$] and correlated (Pearson's r) with climatic variables and indices for each site and compartment. Resistant fractions to tebuconazole and voriconazole were summarized with site-wise boxplots.

Airborne *A. fumigatus* loads correlated negatively with temperature and solar radiation in Dracena ($r \approx -0.9$, $p < 0.01$) and Pereira Barreto (−0.4 to −0.6), reflecting suppression under hot, high-radiation, and dry conditions. Jaboticabal showed a moderate positive association with rainfall ($r \approx 0.6$), whereas irrigated Três Fronteiras exhibited a humidity-driven response ($r \approx 0.5$) with reduced dependence on rainfall, consistent with moisture stabilization by irrigation. Soil populations displayed strong positive correlations with rainfall and temperature ($r = 0.6$–0.8, $p < 0.05$) and peaked in warm, wet months. Across all sites, FFI correlated positively with both airborne and soil abundances (mean $r = 0.63 \pm 0.18$), whereas CSI showed inverse trends (mean $r = -0.52 \pm 0.20$), validating these indices as integrative predictors of fungal favorability versus climatic stress.

This multi-site dataset reveals that *A. fumigatus* thrives under mild, humid, and well-watered conditions but declines sharply under heat-radiative stress. Irrigation partially mitigates atmospheric desiccation, decoupling humidity from rainfall dependence. The standardized FFI and CSI metrics provide quantitative, scalable indicators for real-time modeling of fungal favorability in agricultural environments, contributing to One Health early-warning systems for antifungal resistance surveillance under the FAILSAFE initiative.

Keywords: Aerobiology, climatic indices, irrigation, fungal ecology, antifungal resistance, One Health.

Palavras-chave: Aerobiologia, índices climáticos, irrigação, ecologia fúngica, resistência antifúngica, Saúde Única.

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CLIMATE CHANGE IMPACTS ON FUNGAL PATHOGENS / Impactos das mudanças climáticas em patógenos fúngicos.

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ABSTRACT: Climate change is reshaping fungal ecology, with temperature shifts of up to 6 °C projected in many regions. These changes accelerate fungal adaptation, directly affecting agriculture, food security, and human health. In addition, changing environments cause expansion and contraction of habitable areas for many fungal pathogens. Moreover, intensified fungicide use are

reshaping fungal ecology in ways that bridge agriculture and human health. *Aspergillus* species provide a key model for understanding these dynamics due to their ecological flexibility, agricultural importance, and role as human pathogens. In this presentation, I will (1) summarise how climate-driven range shifts of fungal species may redraw zones of crop–fungus and fungus–human interactions, (2) show laboratory models to study soil fungal interactions, including fungicide exposure and (3) highlight how fungicide selection pressure can accelerate resistance emergence in opportunistic pathogens. *Aspergillus* stands out because it connects agricultural practices with clinical outcomes in a direct and measurable way. Recent work shows that exposure of *Aspergillus fumigatus* to the novel agrochemical fungicide ipflufenoquin can select for cross-resistance to the clinical antifungal olorofim via point mutations in dihydroorotate dehydrogenase (DHODH), with no obvious fitness cost *in vitro* (1). This work highlights that novel antifungal classes can already be impacted by fungicide use in the environment. My contribution to the manifesto stresses that effective responses require linking agronomic policy, ecologic monitoring, and public health foresight, using *Aspergillus* as a case study of microbe adaptation at the agricultural–clinical interface.

Keywords: climate change; fungal ecology; cross-resistance; DHODH; Ipflufenoquin.

Palavras-chave: mudanças climáticas; ecologia fúngica; resistência cruzada; DHODH; Ipflufenoquin.

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WIDESPREAD AZOLE RESISTANCE AND CO-RESISTANCE TO A CLINICAL DHODH INHIBITOR IN *Aspergillus fumigatus* FROM FUNGICIDE-INTENSIVE BRAZILIAN AGROECOSYSTEMS / Resistência generalizada a azóis e co-resistência a um inibidor clínico de DHODH em *Aspergillus fumigatus* de agroecossistemas brasileiros intensivamente tratados com fungicidas.

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ABSTRACT: The rapid emergence of azole-resistant *Aspergillus fumigatus* (ARAf) represents an escalating One Health crisis directly linked to agricultural fungicide use, which has transformed croplands into resistance reservoirs over the past two decades (2). As a major agricultural producer, Brazil has experienced a nine-fold increase in fungicide sales since 2000, dominated by high-risk triazoles (2). This sustained fungicide exposure is hypothesized as the primary driver for widespread azole resistance in environmental fungi (3), a threat corroborated by clinical and environmental surveillance in Brazil that reveals a progressive increase in azole MICs and the emergence of resistant strains carrying novel *cyp51A* mutations (6, 7, 9).

In this study, four fungicide-stressed sugarcane agroecosystems—in Dracena, Jaboticabal, Pereira Barreto, and Três Fronteiras counties—were monitored. A total of 1,702 airborne and 574 soilborne *A. fumigatus* colonies were enumerated and screened for growth on tebuconazole (8 ppm) or voriconazole (4 ppm). The average resistant fraction was 38.6% for tebuconazole and 21.5% for voriconazole. We randomly selected 156 environmental *A. fumigatus* isolates from air and soil for phenotypic characterization of the minimum inhibitory concentration (MIC) using the EUCAST broth microdilution method (E.DEF 9.3) against azoles (tebuconazole and voriconazole) and the novel clinical DHODH inhibitor olorofim (1).

Among these 156 EUCAST-tested isolates, high levels of azole resistance ($MIC_{tebuconazole} \geq 4–64\ \mu g\ mL^{-1}$; $MIC_{voriconazole} \geq 2–64\ \mu g\ mL^{-1}$) were prevalent. The most significant finding was the high frequency (47.4%) of isolates exhibiting co-resistance to both azole classes and the DHODH inhibitor olorofim, a phenotype detected across all sampled sites. This is particularly critical given that there is no history of agricultural deployment of a DHODH inhibitor fungicide—ipflufenoquim—in Brazil, as its official registration only occurred in mid-2025. While widespread azole resistance is an expected outcome of systemic triazole selection pressure (2, 3), the concurrent resistance to the clinical DHODH inhibitor olorofim was unexpected.

This co-resistance pattern strongly suggests that chronic triazole exposure in the environment may have selected for intrinsic, non-target-site resistance mechanisms—such as efflux pump overexpression or metabolic plasticity (4, 8, 10)—capable of conferring collateral resistance to the DHODH inhibitor class. This intrinsic adaptive process is consistent with the mechanisms described by Ishii et al. (5) for plant pathogens with unaltered DHODH target sites.

The detection of *A. fumigatus* co-resistant to azoles and a DHODH inhibitor in Brazilian sugarcane agroecosystems represents a pivotal shift in the environmental landscape of antifungal resistance. It demonstrates that historical triazole use not only sustains azole-resistant populations but can also drive pre-emptive co-resistance to new antifungal classes. This discovery underscores the systemic failure of fungicide resistance management (2) and the urgent need for integrated, cross-sector surveillance connecting plant protection and medical mycology.

Keywords: Environmental surveillance; fungicide resistance management; cross-resistance; non-target-site mechanisms, invasive Aspergillosis; One Health

Palavras-chave: Vigilância ambiental; Manejo da resistência a fungicidas; resistência cruzada; mecanismos de resistência não-alvo; aspergilose invasiva; Uma Só Saúde

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THE *Candida auris* CASE: ANTIFUNGAL RESISTANCE IN YEAST FROM A ONE HEALTH PERSPECTIVE / O Caso *Candida auris*: Resistência antifúngica em leveduras sob a perspectiva da Saúde Única.

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ABSTRACT: Agricultural use of azoles has been strongly associated with the emergence of antifungal resistance in *Aspergillus fumigatus*. However, less attention has been given to pathogenic yeasts that also inhabit the environment, such as the emerging pathogen *Candida* (*Candidozyma*) *auris* (1). This species is frequently linked to hospital outbreaks and displays high rates of antifungal resistance and multidrug resistance, with fluconazole (FCZ) resistance being the most prevalent (77%) (2). One of the main challenges regarding *C. auris* is understanding how its resistance mechanisms evolved. A key hypothesis is that extensive environmental use of agricultural azoles may select resistant isolates that subsequently infect humans (3). Our studies aim to investigate whether exposure to the agricultural azole tebuconazole (TBZ) could select for cross-resistance to FCZ, and to assess the role of temperature in this adaptive process. Susceptibility testing to FCZ and TBZ was performed on thirty-nine *C. auris* isolates following CLSI guidelines. Notably, 94% (15/16) of FCZ-resistant isolates also exhibited elevated MIC values for TBZ, indicating cross-resistance in nearly all cases. This appears to be a distinctive feature of *C. auris*, since our group has previously shown that cross-resistance between FCZ and TBZ is below 10% in the five most common *Candida* species (*C. albicans, Nakaseomyces glabratus, Pichia kudriavzevii, C. tropicalis,* and *C. parapsilosis*) (4). These findings support the hypothesis that environmental azole use may contribute to the emergence of clinical resistance in *C. auris*. To further explore this, *in vitro* exposure experiments with TBZ were conducted using three isolates susceptible to both FCZ and TBZ, originating from distinct geographic regions. The isolates were serially passaged (10 passages) in duplicate at fixed TBZ concentrations (16× MIC) under two temperature conditions (30 °C and 35 °C). This serial exposure led to a progressive increase in MICs for both TBZ and FCZ in all strains, particularly at higher temperature, suggesting that thermal stress enhances the selection of resistant phenotypes. Phenotypic stability of the resistance was tested through subsequent passages in drug-free medium, revealing transient cross-resistance in all isolates. Interestingly, although fixed TBZ exposure did not appear to directly select FCZ-resistant mutants, pre-exposed cells that reacquired FCZ susceptibility required only 3 passages in FCZ to develop resistance to this clinical azole, compared with 6 passages in cells that had never been exposed to TBZ. This indicates that prior TBZ exposure primes cells to more rapidly acquire FCZ resistance. Additionally, experiments with stepwise increases of TBZ concentrations (up to 256 µg/mL) demonstrated that some colony groups acquired permanent cross-resistance even after removal of selective pressure, showing that in this case, FCZ-resistant mutants could indeed be selected by TBZ exposure. Altogether, these results demonstrate that TBZ exposure can induce either stable or transient FCZ resistance in *C. auris*, depending on the concentration of TBZ, and that thermal stress enhances resistance acquisition. Furthermore, evidence indicates that TBZ may prime cells to develop FCZ resistance more rapidly during possible treatment with this drug in the host. To our knowledge, this is the first study highlighting the role of agrochemicals in the selection and persistence of resistance in *C. auris*.

Keywords: *Candida auris*; cross-resistance; tebuconazole; fluconazole; thermal stress.

Palavras-chave: *Candida auris*; resistência cruzada; Tebuconazol; fluconazol; estresse térmico.

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THE *Candida parapsilosis* CASE – ANTIFUNGAL RESISTANCE UNDER ONE HEALTH / O caso *Candida parapsilosis* – resistência antifúngica sob a perspectiva da Saúde Única.

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ABSTRACT: *Candida parapsilosis* is an ascomycetous yeast widely recognized as an opportunistic pathogen (1). Commonly found as a commensal of human skin, it nevertheless accounts for the second to third most frequent cause of candidemia worldwide, particularly in neonatal and intensive care units. Its diploid genome, characterized by a relatively low heterozygosity, complicates population genetics and resistance tracking (2, 3). Reflecting its clinical and epidemiological importance, *C. parapsilosis* was recently included in the World Health Organization fungal priority pathogens list, underscoring its emerging global significance (4, 5). In recent years, a worrying global increase in azole resistance in *C. parapsilosis* has been reported (6, 7). Fluconazole-resistant strains are now responsible for hospital outbreaks on several continents, posing a therapeutic challenge given the limited antifungal armamentarium (6, 8). Many of these outbreaks are clonally driven, with genetic analyses demonstrating persistence and transmission of resistant lineages within and between hospitals (9, 10, 11). This situation raises a central question: is the current rise in resistance only driven by antifungal exposure in clinical settings, or could environmental pressures also contribute, as convincingly demonstrated for *Aspergillus fumigatus*? In this mold, resistance has largely emerged through environmental exposure to agricultural azoles, with resistant spores subsequently infecting azole-naïve patients. Recent reviews asked whether similar selective pressures could also affect pathogenic yeasts (12, 13, 14). In this presentation, we will use the *A. fumigatus* model as a framework to explore whether a comparable scenario may apply to *C. parapsilosis* (15). Specifically, we will review the following questions: (i) does *C. parapsilosis* exist outside clinical settings where fungicide exposure might occur? (ii) are azole-resistant isolates found in environmental niches? (iii) is there evidence of genetic relatedness between environmental and clinical strains? (iv) do resistant infections occur in patients with no prior antifungal exposure? (v) do resistant isolates display cross-resistance between agricultural and medical azoles, and what are the underlying molecular mechanisms? Given the considerable global burden of yeast infections, elucidating the potential role of agrochemical compounds in driving resistance in *C. parapsilosis* and related species is a critical priority that will require integrated epidemiological, environmental, and genomic investigations. More broadly, this underscores the need to expand the One Health framework beyond molds to encompass yeasts, recognizing that antifungal resistance is not confined to clinical settings but is also shaped by wider ecological and agricultural practices.

Keywords: *Candida parapsilosis*; yeast; fluconazole resistance; outbreaks; environmental selection.

Palavras-chave: *Candida parapsilosis*; levedura; resistência ao fluconazol; surtos; seleção ambiental.

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ANTIFUNGAL RESISTANCE IN LIVESTOCK ANIMALS: A SILENT THREAT TO ONE HEALTH / Resistência antifúngica em animais de produção: uma ameaça silenciosa à Saúde Única.

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Abstract: Antifungal resistance in livestock is a growing concern that affects animal health, food safety, and ecosystem resilience (1). Fungal infections are distributed worldwide and can result in significant economic losses (2). The development of these infections in animals is often linked to environmental exposure and, especially, to individual immune deficiency; most are opportunistic infections (3). In cattle, fungal infections are particularly important causes of placentitis and abortion. The species *Aspergillus fumigatus* is the main cause of bovine mycotic abortion, isolated in approximately 60% to 75% of cases and primarily affecting placental tissue (1). Other species such as *A. niger*, *A. flavus*, *Candida* spp., and zygomycetes are also cited (2, 3). Infection in cattle is often opportunistic and is associated with predisposing factors such as immunosuppression, poor body condition, ruminal acidosis, and the use of antibiotics and corticosteroids (4). The source of infection for fungal abortions is typically the ingestion of moldy silage or grain (5). In poultry production, Aspergillosis, caused by *A. fumigatus* and *A. flavus*, is a common respiratory disease in young broilers and can cause high mortality (50% to 90%) on poultry farms. Birds are infected by inhaling spores (6). The treatment of choice for aspergillosis in veterinary medicine is azole antifungals. However, the global emergence of azole resistance in *A. fumigatus* is a concern. One of the biggest concerns is the use of azole fungicides in agriculture, which share the same molecular target as medical azoles, leading to the selection of resistant strains in the environment that are directly linked to the causes of infections in animals (7). Non-wild-type (NWT) *A. fumigatus* isolates, indicative of resistance, have been reported in livestock animals, including poultry. In the case of poultry, the presence of NWT isolates with resistance to itraconazole, posaconazole, and voriconazole is notable, as azoles are not common or authorized treatments for poultry in Brazil and Europe. This suggests that resistance was acquired environmentally. The prevalence of resistance to triazoles in poultry ranges from 0% to 21%. Studies in the Netherlands, for example, found an overall prevalence of azole resistance of 11.3% in clinical isolates of *A. fumigatus* in cattle. This resistance is often mediated by mutations in the *cyp51A* gene, such as TR34/L98H, which confirms the importance of environmental exposure in the selection of resistance (1, 7). Identifying and monitoring antifungal resistance in livestock animals is crucial to understanding the true role of resistant species in infections within the population. Furthermore, a One Health approach to studies is even more essential to managing the spread of these emerging pathogens. The lack of published related data in Brazil makes it even more challenging to implement specific biosecurity measures on farms and to practice veterinary clinical practices, where veterinarians rarely consider azole resistance as a cause of treatment failure and thus fail to screen for resistance in relevant isolates.

Keywords: veterinary mycology; Livestock; azole resistance; *cyp51A*; environment.

Palavras-chave: micologia veterinária; pecuária; resistência a azóis; *cyp51A*; meio ambiente.

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PESTICIDE REGISTRATION AND REEVALUATION IN BRAZIL: LEGAL FRAMEWORK AND REGULATORY ACTIONS FOR FUNGICIDES / Papel Regulatório da Anvisa no Registro e Reavaliação de Agrotóxicos:: Marco Legal e ações regulatórias para fungicidas.

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ABSTRACT: In Brazil, pesticide registration and evaluation are jointly carried out by three institutions: the Brazilian Health Regulatory Agency (Anvisa), the Brazilian Institute of the Environment and Renewable Natural Resources (Ibama), and the Ministry of Agriculture and Livestock (MAPA), representing the health, environment, and agriculture sectors, respectively. In 2023, the legal framework for pesticides was updated with the publication of Law No. 14,785 (1), which repealed Law No. 7,802/1989 (2). Once a pesticide is registered in Brazil, its validity is indefinite, regardless of the legal framework. On the other hand, reevaluation of registered pesticides may be initiated in cases of suspected

risk to human health, the environment, or agronomic inefficacy. At Anvisa, re-evaluation is governed by Resolução da Diretoria Colegiada (RDC) No. 221/2018 (3). This process involves reviewing the human health safety parameters of a specific active ingredient and its registered pesticide formulations. Triggers for reevaluation include alerts from other regulatory agencies, internal monitoring programs, or submissions via a public form on Anvisa's website by any entity. Once a trigger is identified, it undergoes assessment, admission, and prioritization before a formal reevaluation is launched. The reevaluation process includes a detailed review of toxicological studies, both those submitted by registrants and those available in the scientific literature. Additionally, Anvisa examines national monitoring data on food and water residues, compares these with international data, and reviews poisoning records. Recent evaluations by international bodies are also considered. Reevaluation outcomes may include maintaining the product on the market, imposing specific restrictions, or outright bans. Since 2006, Anvisa has completed 20 pesticide active ingredients reevaluations. As a result, 13 active ingredients have been banned: carbendazim, cyhexatin, carbofuran, endosulfan, phorate, lindane, methamidophos, monocrotophos, paraquat, methyl parathion, pentachlorophenol, prochloraz, and trichlorfon; these active ingredients were used in hundreds of registered products. For six active ingredients (2,4-D, abamectin, acephate, fenthion, glyphosate, and thiram), registrations were maintained, but with restrictions to mitigate identified risks. Only one active ingredient, lactofen, was maintained without any restrictions. Among the banned substances, carbendazim, cyhexatin, pentachlorophenol, prochloraz, and trichlorfon were used as fungicides. The bans were justified based on prohibitive criteria outlined in Decree No. 4074/2002 (4), which includes substances known or presumed to be carcinogenic, mutagenic, toxic for reproduction, or endocrine disruptors. For banned fungicides reproductive toxicity was frequently observed.

Keywords: pesticide regulation; regulatory agency; reevaluation, toxicological evaluation, fungicides

Palavras-chave: regulação de agrotóxicos; agência reguladora; reavaliação; avaliação toxicológica; fungicidas

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EU POLICIES ON ANTIFUNGAL MANAGEMENT / Políticas da UE sobre o manejo de antifúngicos.

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ABSTRACT: The European Food Safety Agency (EFSA) recently published a report on the impact of azole fungicides on azole resistance in *Aspergillus* species, issued by the European Commission, and involving for the first time a multiagency collaboration including the European Centre for Disease Prevention and Control (ECDC), the European Chemicals Agency (ECHA), the European Environment Agency (EEA) and the European Medicines Agency (EMA), with support of the European Commission's Joint Research Centre (JRC) (1). The EFSA report is comprehensive and provides details on azole fungicides that have been authorized for use in European member states, examines evidence that supports a causative link between azole fungicide use and the development of azole-resistant *Aspergillus* disease, reviews drivers for environmental resistance selection and proposes a risk assessment framework for current and new authorizations of azole fungicides. Approximately 10,000 tonnes of azole fungicides for plant protection are sold annually in the EU, accounting for >99% of azoles sold, with azole biocides, industrial azoles, and medical/veterinary azoles making up the remainder. The report lists no less than 23 main priority data gaps and 29 recommendations to address these, including lack of use-data of fungicides, which is a key factor in antimicrobial stewardship. Methodology to assess risk of resistance selection based on predicted no effect concentration for resistance (PNECres) requires further validation and refinement including calculation of PNECres in conditions that better mimic natural environments and that consider multiple fungicide exposure. Better understanding of resistance transmission and spread is required as well as One Health surveillance programs, application of genomics to unravel transmission dynamics and determination of azole residue levels in food, surface water and the environment. As activity of environmental fungicides against human pathogens is not currently part of the authorization process, regulatory actions are needed along with validation of the preliminary risk assessment framework. Although the EFSA report was requested by the European Commission it calls on researchers and funding organizations to address the knowledge gaps and help contain azole pollution and drug resistance selection in fungi. An interdisciplinary approach is needed to find sustainable solutions that allow us to ensure food security alongside preserving effective antifungal treatments for an ever-growing human population.

Keywords: European policy; Risk assessment; Azole fungicides; Regulatory framework; One Health surveillance.

Palavras-chave: Política europeia; Avaliação de risco; Fungicidas azóis; Marco regulatório; Vigilância de Saúde Única.

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ENVIRONMENTAL DAMAGE CAUSED BY PESTICIDES AND THE PATHWAYS TOWARD LEGAL ACCOUNTABILITY / Danos ambientais causados por agrotóxicos e possibilidades de responsabilização.

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ABSTRACT: Environmental damage resulting from the improper use of pesticides in Brazil finds its main instruments of investigation, prevention, and reparation in the Civil Inquiry (Inquérito Civil – IC) and the Public Civil Action (Ação Civil Pública – ACP), both available to the Public Prosecutor's Office. The IC is an extrajudicial investigative procedure intended to gather the elements necessary to verify the existence of injury to diffuse, collective, or indivisible individual rights. It constitutes a preparatory stage that allows the Public Prosecutor's Office to form a basis for decision-making and may result in archiving, an agreement, or the filing of an ACP. The ACP is the appropriate procedural instrument for holding the polluter legally accountable before the courts.

Civil liability for environmental damage in Brazil is objective, based on Article 14, §1 of Law 6.938/1981 and Article 927 of the Civil Code, and guided by the theory of integral risk. Under this framework, the polluter is liable regardless of fault, and the demonstration of a causal link between the activity and the damage is sufficient. Jurisprudence from the Superior Court of Justice (STJ) affirms that the theory of integral risk excludes any excluders of liability and that it is enough to prove that the potentially polluting activity contributed to the damage.

At the international level, the Inter-American Court of Human Rights has recognized the right to an ecologically balanced environment, establishing State

obligations to prevent significant environmental damage, based on precaution, best available science, and mechanisms of regulation, oversight, and reparation (1). Advisory Opinion OC-32/25 further reinforced the need for heightened diligence in the context of the climate emergency, imposing duties of prevention, transparency, social participation, and effective supervision of potentially harmful activities (2). Contentious precedents such as *Lhaka Honhat vs. Argentina*, *La Oroya vs. Peru*, and *Olmedo Bustos vs. Chile* recognized violations of rights to water, food, and a healthy environment in contexts of contamination, and affirmed that States may be required to revise internal norms incompatible with the protection of fundamental rights (3–5).

If adequate accountability does not occur within the Brazilian justice system, violations of the right to a healthy environment allow recourse to the Inter-American jurisdiction, ensuring that State omission does not prevent the protection of affected communities against toxic contamination and its permanent effects on health, biodiversity, and human dignity.

Keywords: Pesticides, environmental liability, Public Civil Action, integral risk theory, Inter-American Court of Human Rights, toxic contamination

Palavras-chave: Agrotóxicos, responsabilidade ambiental, Ação Civil Pública, teoria do risco integral, Corte Interamericana de Direitos Humanos, contaminação tóxica

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THE PACE OF PREVENTION: REGULATORY HURDLES AND THE CHALLENGE OF DEVELOPING CLINICAL ANTIFUNGALS FOR INVASIVE FUNGAL INFECTIONS TO KEEP PACE WITH EMERGING RESISTANCE / O ritmo da prevenção: Obstáculos regulatórios e o desafio de desenvolver antifúngicos clínicos para infecções fúngicas invasivas para acompanhar a resistência emergente.

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Antifungal drug development for invasive fungal infections (IFI) remains challenging since fungi are eukaryotic organisms and, thus, only a limited number of selective targets can be exploited without conferring the risk of significant human toxicity. This has resulted in a restricted number of antifungal drugs with currently only four classes of antifungals approved for the treatment of IFI: polyenes, azoles, echinocandins, and flucytosine. Furthermore, these agents have limitations such as toxicity, intrinsic and on-the-rise acquired resistance, drug-drug interactions, and constraints in administration routes [1, 2, 3]. Consequently, there is a long-standing unmet medical need for new classes of antifungal agents for IFI.

In the last few decades, the regulatory landscape has created opportunities for antifungals to make research and development (R&D) in the area more appealing. In the US, both the GAIN (Generating Antibiotic Incentives Now) and Orphan Drug Acts, as well as Fast Track and Breakthrough designations all potentially apply to new antifungal agents and have led to a renewed interest in the area. Other regulatory tools made available by the US Food & Drug Administration (FDA) to assist sponsors in the clinical development of new antibacterial and antifungal drugs to treat serious diseases, particularly those caused by antimicrobial drug-resistant organisms, are: (i) the guidance for industry on the implementation of Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD) pathway and (ii) the guidance for industry Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases.

Despite these initiatives, clinical development and the path for regulatory approval within a reasonable timeframe remain challenging. Indeed, according to this year's World Health Organization (WHO) report of antifungal agents, only four new antifungal drugs have been approved by regulatory authorities in the United States (US) or the European Union (EU) in the past 10 years. Even more striking is the limited number of antifungal medicines in clinical development: nine in total with only three candidates in the final stage of clinical development and thus closer to the regulatory step potentially leading to approval [4].

The gold-standard randomized controlled trials (RCT) expected for registrational purposes are only feasible for invasive candidiasis and invasive aspergillosis, but enrollment is very slow, particularly for the latter. Enrolment, difficulties with diagnosis, and the choice of an appropriate comparator arm pose further feasibility challenges for antifungal agents targeting resistant pathogens or refractory infections.

In summary, emerging resistance (especially that driven by agricultural use of antifungals) is accelerating the need for new agents. However, the challenges of discovery and development of such agents pose significant questions for new antifungals in discovery or early clinical stage to deliver controlled data for the purposes of regulatory approval.

Keywords: Antifungal drug development; regulatory science; invasive fungal infections; antimicrobial resistance.

Palavras-chave: Desenvolvimento de antifúngicos; ciência regulatória; infecções fúngicas invasivas; resistência antimicrobiana.

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CLINICAL-EPIDEMIOLOGICAL PROFILE OF PATIENTS WITH INVASIVE ASPERGILLOSIS IN PUBLIC HOSPITALS IN CAMPINAS, BRAZIL, IN THE LAST DECADE / Perfil clínico-epidemiológico de pacientes com aspergilose invasiva em hospitais públicos de Campinas, Brasil, na última década.

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ABSTRACT: Invasive aspergillosis (IA) is a life-threatening fungal infection that affects immunocompromised individuals and is associated with persistently high mortality rates. Our study presents a clinical-epidemiological analysis of 76 IA cases diagnosed in public hospitals in Campinas, Brazil, between 2017 and 2025. The cohort primarily comprised immunosuppressed patients (78.9%), with pulmonary disease being the most common presentation (97.3%), and *Aspergillus fumigatus* was the main etiological agent. Despite targeted antifungal therapy being administered to 97.3% of patients, the overall mortality rate was alarmingly high at 69.7%, highlighting the profound challenge this disease poses in clinical settings. While these data depict a

critical hospital-based problem, their full implications can only be understood at the intersection of public health and agricultural practices. The primary treatment for IA relies on triazole antifungal agents; in our cohort, azoles were used in 68.9% of the cases. A significant and growing body of evidence (1) demonstrates a direct link between the extensive use of azole-based fungicides in agriculture and the emergence of panazole-resistant *A. fumigatus* strains in the environment. These resistant strains, selected by agricultural pressures, can be inhaled by susceptible individuals, leading to infections that are refractory to first-line medical drugs. Therefore, our contribution to the final manifesto is to underscore that the management of IA is not solely a clinical issue but a broader "One Health" challenge. The high mortality rate observed in our hospitals may be intrinsically linked to environmental selection pressures driven by local and regional agricultural practices. We advocate the urgent implementation of integrated surveillance programs to monitor antifungal resistance in both clinical and environmental settings. A comprehensive public health strategy must include agricultural stewardship of fungicides to preserve the efficacy of essential life-saving antifungal medications for human use (2). Addressing the root environmental drivers of resistance is paramount to improving outcomes for vulnerable patients. Our contribution to the manifesto emphasizes the urgent need to: (a) expand surveillance programs integrating clinical, environmental, and agricultural data; (b) regulate and monitor agricultural azole fungicide use; (c) strengthen laboratory capacity for early diagnosis and resistance detection; and (d) foster intersectoral policies that embody the One Health perspective. Only through these coordinated strategies can we mitigate the dual threats of agricultural practices that fuel antifungal resistance and the devastating impact on immunocompromised populations.

Keywords: invasive aspergillosis; mortality; One Health; agricultural fungicides; public policy.

Palavras-chave: aspergilose invasiva; mortalidade; Saúde Única; fungicidas agrícolas; política pública.

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RESISTANCE-DRIVEN POLICY: LESSONS FROM A MAJOR PLANT PATHOGEN FOR MANAGING *ASPERGILLUS FUMIGATUS* / Política guiada pela resistência: Lições de um fitopatógeno para o manejo do *Aspergillus fumigatus*.

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ABSTRACT: Fungicide resistance is an increasing challenge in agriculture, threatening the effectiveness of disease management and crop productivity worldwide. In Brazil, soybean is one of the main crops, playing a strategic role in the national economy, accounting for a large portion of the country's exports. Currently, the sown area exceeds 47 million hectares. Disease management in this crop is an escalating challenge. The use of fungicides in soybeans has increased since the detection of *Phakopsora pachyrhizi*, the causative agent of Asian rust, in 2001, and the expansion of soybean to tropical regions of the Cerrado, characterized by a hot climate and frequent rainfall, which favors the occurrence of leaf spots. The average number of fungicide applications per crop cycle (100 - 140 days) is approximately 3.5. The site-specific fungicides used in soybeans belong to three main chemical groups: demethylation inhibitors (DMIs), quinone outside inhibitors (QoIs), and succinate dehydrogenase inhibitors (SDHIs). Reports of fungicide resistance in the crop are frequent, impacting control efficacy. Most fungi occurring in the crop exhibit partial or complete resistance to some chemical group (1, 2, 3, 4, 5). The resistance of *P. pachyrhizi* led to the re-evaluation of fungicides by the Ministry of Agriculture, Livestock and Food Supply (MAPA) in 2016, resulting in the suspension of registrations for fungicides with isolated active ingredients and those with low efficacy, as well as a reduction in the application interval from 21 to 14 days. Fungicide mixtures with multiple modes of action are recommended to delay the selection process of less sensitive isolates. Since 2012, multisite fungicides have been used in soybeans to enhance control efficacy and attempt to reduce the selection of less sensitive populations to site-specific fungicides. For *P. pachyrhizi*, in the case of DMIs, mutations in the *CYP51* gene (F120L, V130A, Y131F/H, K142R, I145V/F, F154Y, I475T) and overexpression are involved in reducing sensitivity. Sensitivity studies also demonstrated incomplete cross-resistance of *P. pachyrhizi* to DMIs, caused by different mutation combinations. Legislative measures are part of disease management in soybean crops in Brazil. The soybean-free period, a period of at least 90 days without the crop during the off-season, is used to reduce the inoculum of the fungus for the following growing season and delay the onset of the soybean rust. Planting windows have been defined to shorten the period the crop remains in the field, aiming to reduce the number of fungicide applications throughout the crop season and delay the selection of less sensitive or resistant populations. The limited number of modes of action and the widespread occurrence of resistant populations make all currently used chemical groups necessary for disease management in the crop. New modes of action are under evaluation; however, the selection of less sensitive populations has occurred faster than the development of new molecules. The selection and use of soybean cultivars with genetic resistance to diseases have been implemented, but these face the same issues of selection pressure and breakdown of resistance due to more aggressive populations.

Keywords: soybean; *Phakopsora pachyrhizi*; DMI; QoI; SDHI; resistance management.

Palavras-chave: soja; *Phakopsora pachyrhizi*; DMI; QoI; SDHI; manejo da resistência.

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THE HONEST BROKER: THE ROLE OF INDEPENDENT SCIENCE IN SHAPING SUSTAINABLE AGRICULTURE FOR PUBLIC HEALTH / O Mediador Científico Imparcial: O papel da ciência independente na construção de uma agricultura sustentável para a saúde pública.

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ABSTRACT: Antimicrobials used to control the growth of fungi—known as antifungals when used in the clinic or fungicides when used in the environment—are essential to control fungal diseases (4). Over 2.5 million people die from fungal infections each year (1), and globally, crop losses due to fungal pathogens exceed 30%, enough to provide food for 600 million people (2). The economic cost of these losses is up to US$200 billion globally (6), with one disease (*Septoria tritici*, which infects wheat) costing $132–264 million in the UK alone (5) (a figure that only includes direct crop losses, not the cost of preventative measures like crop spraying). Fungal antimicrobial resistance (fAMR) is now a major problem worldwide (8). Given the broad use of chemical classes for the protection of human and plant health, it is essential that we sustainably balance fungicide/antifungal use to optimize health across all sectors (3). Although there is strong scientific evidence that fungicide use is contributing to fAMR within

human fungal pathogens (7), changes in policy to protect citizens are slow to be implemented. Efforts need to be made to develop a bespoke, risk-based framework to manage fAMR. Here, I will discuss our efforts in bringing together stakeholders across sectors with policymakers to identify and develop policy and action plans to deal with the complex and unique issues presented by fAMR in the UK and beyond. I will discuss the current EU response to the dual use of azoles, and the scope for implementing change within the current policy landscape.

Keywords: fungal antimicrobial resistance; policy development; sustainable agriculture; stakeholder engagement; One Health.

Palavras-chave: resistência fúngica a antimicrobianos; desenvolvimento de políticas; agricultura sustentável; engajamento de partes interessadas; Saúde Única.

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THE FAO's ROLE IN ADDRESSING ANTIMICROBIAL RESISTANCE IN AGRIFOOD SYSTEMS / O papel da FAO no enfrentamento da resistência aos antimicrobianos em sistemas agroalimentares.

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ABSTRACT: Antimicrobial Resistance (AMR) is one of the current top global health issues (1). Often, it is simplified to the version "resistance to antibiotics" and therefore associated by many only to human health. In reality, its dimensions are much broader, as all antibiotics are antimicrobials, but not all antimicrobials are antibiotics. Antimicrobials, including antifungals, are used not only in human medicine but also in animals and plants/crops, with a spill over to the environment, making it a perfect illustration of a One Health issue (1). In particular after the adoption of the Global Action Plan (GAP) on AMR in 2016, a multitude of initiatives have been implemented at different levels, many of them focusing on: i. raising awareness on AMR; ii. data collection and iii. responsible and prudent antimicrobial use, when needed. AT FAO, the AMR Action Plan has been the overall umbrella, that covered, for example, the development of the InFARM (International AMR Monitoring System) database and the RENOFARM (Reduce the Need for Antimicrobials on Farms for Sustainable Agrifood Systems Transformation) initiative (2). AMR can also be foodborne, and the same can be said the other way around: some of the foodborne infections are caused by antimicrobial resistant microorganisms. The exact dimensions of these phenomena are not quantifiable on a global scale. It is important to emphasize that AMR is also a food safety issue that threatens future global food security. Some of the recent scientific findings challenge previously accepted knowledge regarding 'fitness cost" and the importance of controlling the development vs the transmission of AMR. The implementation of Codex AMR standards is nevertheless instrumental to ensure the protection of public health and fair trade. The cornerstones to control AMR are: 1) a change in behaviors to preserve antimicrobials as global common goods and 2) an agrifood systems transformation that ensures a sustainable food production (3).

Keywords: antimicrobial resistance; agrifood systems; food safety; One Health; FAO.

Palavras-chave: resistência aos antimicrobianos; sistemas agroalimentares; inocuidade dos alimentos; Saúde Única; FAO.

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AZOLE-RESISTANT *ASPERGILLUS FUMIGATUS*: SURVEILLANCE GAPS AND U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION INITIATIVES / Azole-Resistant *Aspergillus fumigatus*: Lacunas na vigilância e iniciativas dos Centros de Controle e Prevenção de Doenças dos EUA.

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ABSTRACT: Surveillance of antifungal resistance in *Aspergillus fumigatus* faces several challenges, including the lack of commercial testing methods, limited laboratory capacity, and challenges with differentiating infection from colonization. Most clinical laboratories do not routinely perform antifungal susceptibility testing (AFST), likely leading to underreporting of resistant cases. Further, environmental reservoirs of *A. fumigatus*, particularly in certain agricultural settings where fungicides are extensively applied, are not well characterized. The extent to which agricultural fungicide use contributes to resistance among clinical isolates remains an area of active study, but emerging evidence suggests it might play an important role (1). Resistant *A. fumigatus* strains carrying mutations associated with environmental fungicide use have been detected as a cause of human infections. However, broad surveillance for such fungicide-associated resistant infections is limited in part due to limited access to advanced diagnostic tools that are needed to detect these mutations (e.g., whole genome sequencing [WGS]). In response to these surveillance gaps, the U.S. Centers for Disease Control and Prevention's (CDC) Mycotic Diseases Branch (MDB) has initiated several programs aimed at improving the detection and management of antifungal resistance in *A. fumigatus*. One key initiative is incorporating *A. fumigatus* testing into CDC's Antimicrobial Resistance Lab Network (AR Lab Network), which allows clinicians and laboratories to send *A. fumigatus* isolates to select labs for AFST and WGS, free of charge. During January 2025–July 2025, 1,640 isolates were tested; 14 had confirmed resistance. This program encourages collaboration among public health agencies, clinical laboratories, and healthcare providers to enhance reporting and understanding of resistance trends. Additionally, MDB has started a national enhanced surveillance program called FungiSurv, which includes azole-resistant *A. fumigatus*. This platform allows state and local health departments to collect in-depth epidemiological data on resistant cases to better understand patient's demographic characteristics, risk factors, exposure, and outcomes. Education and awareness campaigns are another critical component of the MDB's initiatives. By providing resources and training for healthcare professionals and the public, the CDC seeks to improve the recognition of antifungal resistance and the importance of early diagnosis and appropriate treatment. Finally, CDC worked with other federal partners to establish the Interagency Drug and Pesticide Resistance and Efficacy

Workgroup to assess and manage the risks of pesticides, particularly antifungal products, in driving resistance to medically important human and animal drugs in target and non-target fungi. This collaboration allows for a unified "One Health" approach to consider resistance risks (2). The framework aims to balance the agricultural and public health benefits of these pesticides with their potential to induce antifungal resistance. In conclusion, addressing the surveillance gaps in antifungal resistance for *A. fumigatus* is essential for guiding public health action. MDB's surveillance initiatives enhance epidemiological understanding, promote responsible antifungal use, and foster research and education. Continued efforts are necessary to monitor resistance trends, develop effective interventions, and ultimately reduce the burden of antifungal-resistant infections. As the landscape of fungal infections evolves, a multisectoral response will be crucial in mitigating the impact of *A. fumigatus* and ensuring effective treatment options remain available.

Keywords: antifungal resistance; surveillance; One Health; public health; azoles.

Palavras-chave: Resistência fúngica; Vigilância; Saúde Única; Saúde Pública; Azóis.

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THE BRAZILIAN MINISTRY OF HEALTH PERSPECTIVE ON ONE HEALTH AND ANTIFUNGAL RESISTANCE / A perspectiva do Ministério da Saúde do Brasil sobre Saúde Única e resistência antifúngica.

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ABSTRACT: Fungal infections represent a major global health problem, affecting billions of people and causing more than 1.7 million deaths annually (1). In Brazil, antifungal resistance has emerged as a public health concern in the context of a growing incidence of opportunistic infections, such as aspergillosis, particularly among immunocompromised patients (1, 2). Because environmental fungi are frequently exposed to antifungals, resistance arising in this context is likely to directly impact the clinical management of infections (3). To address this challenge, the Brazilian Ministry of Health has incorporated antifungal resistance into national surveillance strategies within the One Health framework. Among these actions, the publication of the National Action Plan for the Prevention and Control of Antimicrobial Resistance (PAN-BR), which aims to prevent and control antimicrobial resistance, stands out (4). In addition, the Brazilian Ministry of Health conducts laboratory surveillance of fungal infections through the National Public Health Laboratory Network and has introduced new diagnostic technologies into the Unified Health System (SUS), such as those for cryptococcosis and histoplasmosis (5, 6, 7). To ensure timely and equitable access to antifungal therapies, the Brazilian Ministry of Health centrally provides essential drugs, including itraconazole, liposomal amphotericin B, amphotericin B lipid complex, flucytosine, anidulafungin, isavuconazole, and voriconazole, thereby expanding therapeutic options for the treatment of endemic and opportunistic mycoses, such as aspergillosis, in the context of resistance (8). Given that endemic and opportunistic mycoses are not nationally notifiable diseases, with the exception of human sporotrichosis, the Brazilian Ministry of Health developed the Information System for Endemic and Opportunistic Mycoses, which is currently being implemented in SUS referral services that manage these mycoses. This system integrates the process of surveillance implementation across all states, linking epidemiological reporting to clinical follow-up with the aim of ensuring appropriate treatment and timely access to antifungals through the structuring of state-level care networks. To strengthen the capacity of health professionals in managing endemic and opportunistic mycoses, the Brazilian Ministry of Health has promoted training courses and produced guidelines, manuals, and surveillance protocols, thereby reinforcing the health system's response and contributing to antifungal resistance control through rational prescribing, improved diagnostic accuracy, and the standardization of clinical practices. Furthermore, the Brazilian Ministry of Health participates in research initiatives aimed at monitoring antifungal resistance, such as VigRAM, focused on detecting multidrug-resistant *Candida* in hospitals, and ReNaRAn, dedicated to monitoring endemic and opportunistic systemic mycoses within the SUS. These initiatives consolidate the integration of epidemiological, laboratory, and clinical surveillance, enhancing the SUS's capacity to respond to endemic and opportunistic mycoses. Collectively, they represent a strategic advance in combating antifungal resistance, aligned with the principles of the One Health approach.

Keywords: public health policy; National Action Plan; health surveillance; Unified Health System; access to medicines.

Palavras-chave: política de saúde pública; Plano de Ação Nacional; vigilância em saúde; Sistema Único de Saúde; acesso a medicamentos.

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PUBLIC POLICIES FOR THE RATIONAL USE OF FUNGICIDES AND COMBATTING ANTIMICROBIAL RESISTANCE / Políticas públicas para o uso racional de fungicidas e combate à resistência antimicrobiana.

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ABSTRACT: The **Decreto nº 12.007/2024** (1) established the Interinstitutional Technical Committee for One Health, a federal advisory body to promote an integrated approach to human, animal, plant, and environmental health. The committee aims to develop a National One Health Action Plan and strengthen cooperation between different ministries, agencies, and entities to address challenges such as pandemics and antimicrobial resistance. The National Action Plan for the Prevention and Control of Antimicrobial Resistance (AMR) in Agriculture (PAN-BR AGRO) (2), developed by the Ministry of Agriculture, has as a strategic intervention the development of a system for monitoring antimicrobial use in agriculture, a measure linked to the UN Sustainable Development Goals (SDGs) 2, 3, and 6. Other public policies support the rational use of fungicides and the fight against AMR (3). The Ministry of Agriculture,

Livestock and Food Supply (MAPA) is responsible for regulating, standardizing, and inspecting fungicides in Brazil, including their registration, release, and use. The Brazilian Agricultural Research Corporation (Embrapa) and other research institutions work on developing strategies for resistance management, including the correct use of products, the diversification of control strategies, and the use of bio-inputs and other sustainable alternatives to reduce AMR.

Keywords: public policies; PAN-BR AGRO; rational use; resistance management; bioinputs.

Palavras-chave: políticas públicas; PAN-BR AGRO; uso racional; manejo da resistência; bioinsumos.

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ASPERGILLUS FUMIGATUS IN THE FOOD PRODUCTION CHAIN AND AZOLE RESISTANCE / *Aspergillus fumigatus* na cadeia produtiva de alimentos e resistência a azóis.

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ABSTRACT: *Aspergillus fumigatus* is a fungus of great public health relevance, recently included by the World Health Organization in the critical priority group of fungal pathogens. It is the causative agent of aspergillosis, a disease with mortality rates that can reach 50-100% in its invasive forms. Treatment for this infection relies on azole antifungals; however, its efficacy is threatened by increasing resistance, often linked to specific mutations in the *Cyp51A* gene. Beyond selective pressure in clinical settings, an environmental resistance pathway is strongly emerging, driven by the extensive use of azole fungicides in agriculture. This microorganism enters the food production chain from crop fields and can contaminate a wide range of foods such as cereals, legumes, coffee, cocoa, spices, and nuts. Postharvest processes such as drying, fermentation, and storage are critical stages where temperature and humidity conditions favor the proliferation of this thermotolerant fungus. Thus, food becomes a potential vehicle for human exposure to *A. fumigatus*, constituting a silent threat. This work explores how the food chain acts as a bridge between agricultural practices and a direct risk to consumer health. It analyzes the sources of contamination and the implications for food safety, highlighting the urgency of investigating whether the ingestion of spores contributes to human colonization or infection and of adopting integrated surveillance and control strategies to mitigate this growing challenge (1).

Keywords: food safety; food chain; contamination; *Cyp51A*; consumer health.

Palavras-chave: inocuidade dos alimentos; cadeia alimentar; contaminação; *Cyp51A*; saúde do consumidor.

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TECHNICAL GUIDANCE FOR THE MEETING'S WORKING GROUPS: A ONE HEALTH FRAMEWORK FOR ASSESSING FUNGICIDE ESSENTIALITY / Orientação Técnica para os Grupos de Trabalho: Um Marco de Saúde Única para avaliar a essencialidade de fungicidas.

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ABSTRACT: The accelerating threat of antifungal resistance demands an integrated One Health response that evaluates agricultural fungicide use through its impacts on human, animal, and environmental health. To support deliberations during the Brazilian Network Meeting on *Aspergillus fumigatus* Antimicrobial Resistance, we present a technical framework designed to guide Workgroups A–D in assessing the essentiality of fungicides using harmonized, evidence-based criteria.

Using a nationwide dataset of publicly available fungicide trials (2023–2024) in maize, soybean, cotton, and wheat, we developed two quantitative indicators: (i) an Agronomic Score (A), defined as the joint probability of achieving both a meaningful yield gain (>10%) and positive economic return; and (ii) a One Health Sustainability Score (OHS), integrating human/animal AMR risk (OHS_H) and the risk of resistance evolution in agricultural pathogens (OHS_P), based on the FRAC mode-of-action classification. Together, these scores provide an objective basis for evaluating whether any fungicide strategy delivers reliable agronomic benefit while maintaining a low risk of contributing to antimicrobial resistance in clinical and agricultural pathogens.

We operationally define a fungicide or fungicide strategy as "essential" only when it satisfies both conditions: (1) high agronomic reliability, expressed as a sufficiently high Agronomic Score (A), and (2) high One Health sustainability, reflected in an OHS indicating low AMR risk to human and animal health and a low likelihood of resistance evolution in agricultural pathogens. Failure in either dimension renders a fungicide non-essential within this framework. This definition broadens fungicide evaluation beyond yield outcomes and places public health protection at the center of essentiality determinations.

Analyses reveal that, across crops, no fungicide strategy consistently achieved high agronomic reliability, with median disease control around 60% and most strategies clustering between 50–70% even under optimal conditions. Multi-site strategies performed comparably to multi-component single-site mixtures, and the added complexity of mixtures did not guarantee superior or stable performance. These findings underscore that agronomic outcomes alone cannot justify the designation of fungicides as essential, particularly when weighed against their documented potential to select for resistance in both plant pathogens and *Aspergillus fumigatus*, a major human pathogen.

This framework offers the Working Groups a structured, quantitative, and policy-neutral foundation for deliberation. It supports the identification of fungicide uses that align with One Health principles and can inform a consensus on the Public Motion for Health-First Fungicide Policies, to be finalized and voluntarily endorsed during the meeting's closing session. By integrating agronomic evidence with AMR risk considerations, this approach seeks to realign fungicide policy discussions with the overarching societal goal of safeguarding public health.

This framework is now made available to the Working Groups for critical scrutiny and refinement, supporting the collaborative development of the Public Motion for Health-First Fungicide Policies.

We therefore invite all Working Groups to critically examine, challenge, and refine this framework during their deliberations, ensuring that any conclusions and recommendations emerging from this meeting are collectively built, transparently justified, and firmly grounded in the best available evidence.

Keywords: One Health; fungicides; antimicrobial resistance; essentiality criteria; agronomic reliability; policy frameworks

Palavras-chave: Saúde Única; fungicidas; resistência a antimicrobianos; essencialidade; desempenho agronômico; políticas públicas

POSTERS

Brazilian Network Meeting: *Aspergillus fumigatus* Antifungal Resistance – Protecting Health in the Face of Agricultural Pressures

COMPUTATIONAL INSIGHTS INTO ANTIFUNGAL RESISTANCE AND BIOECOLOGY OF *ASPERGILLUS FUMIGATUS*: A ONE HEALTH PERSPECTIVE / Percepções computacionais sobre resistência antifúngica e bioecologia de *Aspergillus fumigatus*: uma perspectiva de Uma Só Saúde.

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ABSTRACT: *Aspergillus fumigatus* poses a significant threat to human, animal, and environmental health due to its ecological adaptability and rising antifungal resistance. Agricultural fungicide use has been recognized as a major driver of resistance development, yet the molecular mechanisms linking environmental exposure to clinical resistance remain incompletely understood. In this study, we employed computational approaches—including molecular docking, molecular dynamics simulations, and network pharmacology—to investigate the structural basis of resistance mechanisms in *A. fumigatus*. Docking and simulation studies revealed altered binding interactions between azole antifungals and mutated forms of the CYP51A enzyme, clarifying how specific substitutions reduce drug efficacy. Network-based analyses further mapped interactions between resistance-associated genes and environmental stress response pathways, highlighting potential surveillance biomarkers. By integrating bioecological insights with computational modeling, our findings demonstrate how agricultural practices contribute to antifungal resistance and propose *in silico* strategies to support mitigation. This poster underscores the relevance of computational pipelines in resistance surveillance, risk assessment, and therapeutic innovation, aligning with the One Health approach to safeguard human, animal, and environmental well-being.

Keywords: molecular docking; molecular dynamics; CYP51A; network pharmacology; azole resistance.

Palavras-chave: docking molecular; dinâmica molecular; CYP51A; farmacologia de rede; resistência a azóis.

DISCOVERY OF PROMISING DRUGS FROM BRAZILIAN BIODIVERSITY TO MITIGATE *ASPERGILLUS FUMIGATUS* RESISTANCE / Descoberta de fármacos promissores da biodiversidade brasileira para mitigar a resistência de *Aspergillus fumigatus*.

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ABSTRACT: The rise of *A.fumigatus* resistance, largely driven by intensive agricultural fungicide use, represents a pressing public health concern. Mortality from invasive aspergillosis exceeds 50%, reaching up to 90% in transplant recipients, reinforcing the urgent need for mitigation strategies. Drug discovery from natural sources remains a promising approach, and Brazil's microbial biodiversity stands out as an invaluable reservoir. In this study, we investigated two actinomycete strains isolated from Brazilian ecosystems: CBMAI-3036 (*Nocardiopsis dassonvillei*) and CBMAI-3038 (*Streptomyces* sp.). Bacterial extracts were tested using broth microdilution assays against clinical *A.fumigatus* isolates, comprising one susceptible reference strain and five resistant isolates, including three with CYP51A mutations and two with resistance mechanisms not linked to CYP51A. Both extracts displayed broad-spectrum antifungal activity, with CBMAI-3038 showing MIC values of 0.125 mg/mL against all isolates and MIC=0.5 mg/mL for CBMAI-3036. To identify the metabolites responsible for this activity, we combined metabolomic profiling with genome mining using antiSMASH. Metabolomic analysis of the bacterial extracts, performed through the GNPS platform, revealed puromycin in CBMAI-3038, and a phenazine derivative in CBMAI-3036. Biosynthetic gene clusters predicted to encode puromycin and phenazine were detected in the respective genomes. These results account for the bioactivity observed and highlight three candidate molecules for drug discovery. Ongoing work focuses on compound isolation and toxicity evaluation to assess their potential as therapeutic leads. Importantly, even if pharmacological properties ultimately limit clinical application, these strains and their metabolites also hold promise for agricultural biocontrol strategies. Such applications could reduce reliance on azole fungicides, mitigating major drivers of *A. fumigatus* resistance while promoting sustainable practices. Brazil's agricultural model, dominated by monocultures and permissive fungicide use, raises public health concerns. At the same time, this model threatens the country's exceptional biodiversity, whose conservation is crucial for ecological balance and as a reservoir of bioactive compounds.

Keywords: actinomycetes; natural products; drug discovery; biocontrol; microbial biodiversity.

Palavras-chave: actinomicetos; produtos naturais; descoberta de fármacos; biocontrole; biodiversidade microbiana.

AZOLE RESISTANCE IN *ASPERGILLUS FUMIGATUS*: EVIDENCE FROM 23 YEARS SURVEILLANCE / Resistência a azóis em *Aspergillus fumigatus*: evidências de 23 anos de vigilância.

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ABSTRACT: Azole resistance in *Aspergillus fumigatus* compromises the effectiveness of standard antifungal therapies and may arise during prolonged azole treatment or from environmental exposure to azole fungicides. This study spans 23 years (1998–2021) of clinical isolates, characterizing cases with *cyp51A* mutations versus those exhibiting phenotypic resistance without known mutations. A total of 619 clinical isolates of *A. fumigatus* sensu stricto obtained at HC-UNICAMP were analyzed. Antifungal susceptibility was assessed by broth microdilution, and isolates with elevated azole MICs were sequenced for the *cyp51A* gene. Among the isolates, 1.2% showed MICs>2µg/mL for itraconazole, 3.4% for voriconazole, and 2% >0.5mg/mL for posaconazole, with no echinocandin resistance detected. Classical resistance mutations were identified, including TR34/L98H/S297T/F495I, TR46/F495I, and G448S, along with polymorphic substitutions. G448S occurred in isolates from patients with voriconazole treatment failure, indicating acquired resistance, whereas TR34/L98H/S297T/F495I and TR46/F495I in isolates without prior clinical exposure suggest a likely environmental origin. This interpretation is supported by the recovery of G448S isolates from active infections, while TR34 isolates were obtained from colonized patients without evidence of disease. An isolate carrying

the TR46 mutation was collected directly from the environment of an ICU room, further supporting these findings. Continuous surveillance of *A. fumigatus* is crucial for the early detection of resistance mutations, guiding effective antifungal therapy, and preventing the spread of resistant strains.

Keywords: antifungal susceptibility; *cyp51A*; TR34/L98H; TR46; surveillance.

Palavras-chave: susceptibilidade antifúngica; *cyp51A*; TR34/L98H; TR46; vigilância.

THE EXPANDED USE OF BIOFUNGICIDES AS A KEY STRATEGY TO MITIGATE AGRICULTURE-DRIVEN ANTIFUNGAL RESISTANCE IN *ASPERGILLUS FUMIGATUS* / O uso ampliado de biofungicidas como estratégia-chave para mitigar a resistência a antifúngicos em *Aspergillus fumigatus* impulsionada pela agricultura.

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ABSTRACT: The emergence of azole-resistant *Aspergillus fumigatus* is a critical One Health challenge, driven largely by the widespread use of azole fungicides in agriculture. These agents exert strong environmental selection pressure, leading to cross-resistant strains that compromise clinical treatment of invasive aspergillosis. This study analyzes the broader agricultural pesticides market—encompassing chemical, microbial, and semiochemical products—to advocate for the expanded use of microbial biofungicides as a primary mitigation strategy. Biofungicides market data from Brazil (IBAMA, 2025) reveals a pronounced structural shift within this market: the microbial and semiochemical segment grew at a CAGR of 26.50% (2014–2023), nearly double that of the chemical pesticides segment (14.76%). This rapid growth and the concurrent surge in unique active ingredient registrations signal a strong market transition towards low-resistance-risk alternatives. Within this biological segment, biofungicides constitute a substantial and growing portion (~22% of unique microbial active ingredients), dominated by *Bacillus* and *Trichoderma* strains. These agents employ complex, multi-site modes of action with no overlap with clinical azoles, presenting a low-risk resistance profile. The documented expansion and diversification of the biofungicide portfolio within the agricultural pesticides market provide a clear, evidence-based pathway for reducing environmental azole selection pressure, thereby preserving the efficacy of medical antifungals.

Keywords: antifungal resistance; biofungicides; *Aspergillus fumigatus*; azole resistance; One Health; pesticide market.

Palavras-chave: resistência a antifúngicos; biofungicidas; *Aspergillus fumigatus*; resistência a azóis; Uma Só Saúde; mercado de pesticidas.

CONTRASTING SENSITIVITY OF *ASPERGILLUS NIGER* TO AZOLE AND STROBILURIN FUNGICIDES IN ONION BLACK MOLD MANAGEMENT / Sensibilidade contrastante de *Aspergillus niger* a fungicidas azóis e estrobilurinas no manejo do mofo-preto da cebola

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ABSTRACT: The management of onion black mold, caused by *Aspergillus niger*, relies on fungicides, but their continued use risks selecting for resistant populations. This study investigated the *in vitro* sensitivity of *A. niger* isolates to different chemical classes. The pathogen was isolated from infected onions and its sensitivity was tested on PDA medium amended with two triazole (F1-difenoconazol, F2-tebuconazol) and one strobilurin (F3-azoxistrobina+difenoconazol) fungicide, each applied at half, full, and double the recommended dose. After a seven-day incubation period, mycelial growth inhibition was calculated. A significant interaction ($p < 0.05$) between fungicide and dose was observed. The isolates exhibited a marked contrast in sensitivity. High sensitivity was observed against the triazole fungicide F2, which caused the strongest growth inhibition, particularly at the full dose. An intermediate sensitivity was found for the triazole F1. In stark contrast, the isolates showed markedly reduced sensitivity to the strobilurin+triazole fungicide (F3), which resulted in minimal inhibition even at the highest dose. These results demonstrate a clear differential sensitivity in *A. niger* populations, with effective control offered by a specific triazole, while revealing significant insensitivity to the strobilurin, underscoring a critical resistance risk that necessitates tailored anti-resistance strategies.

Keywords: *Allium cepa*; azole; chemical control; fungicide resistance; strubilurin.

Palavras-chave: *Allium cepa,* azóis, controle químico, resistência *à* fungicidas, estrubilurinas

A ONE HEALTH ASSESSMENT OF *ASPERGILLUS FUMIGATUS* IN BRAZILIAN DRY FOODS REVEALS HIGH PREVALENCE AND GENETIC DIVERSITY WITHOUT AZOLE RESISTANCE / Uma abordagem de saúde única para *Aspergillus fumigatus* em alimentos secos brasileiros revela alta prevalência e diversidade genética sem resistência a azóis

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ABSTRACT: *Aspergillus fumigatus* is a ubiquitous saprotrophic fungus and the primary cause of aspergillosis, a disease that develops mostly from the inhalation of spores. While the environment is considered the main source of exposure, dry food products can serve as secondary reservoirs, as spores can become aerosolized during handling. This study aimed to determine the prevalence and azole sensitivity of *A. fumigatus* in common Brazilian dry foods to assess their potential role in exposure. We examined 25 commercial samples of yerba mate, black pepper, and green coffee, successfully isolating *A. fumigatus* from 68% of them, yielding 42 isolates. All isolates exhibited EC_{50} values below clinical resistance thresholds for tebuconazole (0.04–0.70 µg/mL), itraconazole (0.06–0.59 µg/mL), and voriconazole (0.08–0.15 µg/mL). *CYP51A* sequencing identified only the M172V polymorphism, which is not associated with resistance. Microsatellite genotyping revealed high genetic diversity, with 33 multilocus genotypes identified among the 42 isolates. A minimum-spanning network showed high connectivity and limited population structure, indicating shared environmental sources and genetic exchange. The high prevalence and substantial genetic diversity of *A. fumigatus* in these dry foods confirm that they act as carriers of environmentally derived spores. These findings underscore the need for integrated One Health surveillance to detect shifts in *A. fumigatus* populations and anticipate emerging risks at the interface of agriculture, food safety, and public health.

Keywords: *Aspergillus fumigatus*, saúde única, alimentos secos, resistência a azóis, diversidade genética.

Palavras-chave: *Aspergillus fumigatus*, One Health, alimentos secos, resistência a azóis, diversidade genética.

PREVALENCE OF *ASPERGILLUS FUMIGATUS* IN COMMERCIAL AND FIELD-LEAF YERBA MATE AND EMERGING AZOLE SENSITIVITY PATTERNS / Prevalência de *Aspergillus fumigatus* em erva-mate comercial e folhas de campo e padrões emergentes de sensibilidade a azóis

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ABSTRACT: Foodborne exposure to *Aspergillus fumigatus* represents an overlooked interface between agricultural environments and human health, particularly in regions with intensive azole fungicide use. Yerba mate (*Ilex paraguariensis*), a native South American species traditionally harvested from extractivist or semi-extractivist systems, is not directly sprayed with fungicides. However, its production often occurs adjacent to intensively treated crops, exposing it to airborne conidia and potential azole selection pressure. We investigated the prevalence of *A. fumigatus* in ten yerba mate samples (nine commercial products and one foliage sample from a Legal Reserve area). The fungus was detected in all samples. Species-level identification was confirmed for all isolates via PCR targeting the β-tubulin and rodA genes. Six representative isolates were evaluated for in vitro sensitivity to tebuconazole. The EC_{50} values revealed a clear bimodal distribution. Isolates (IA19M4, IA11M2, IA10M5.1 and IA10M5.2) were highly sensitive (EC_{50} 0.03–0.05 µg/mL), while two isolates (IA10M4.1 and IA10M2.1) exhibited a resistant phenotype ($EC_{50} \geq 8.0$ µg/mL). No intermediate phenotypes were detected. This is the first report of tebuconazole-resistant *A. fumigatus* isolates in yerba mate. The finding of a resistant phenotype alongside sensitive ones in this untreated crop system provides direct evidence of environmental selection pressure from agricultural azole use. It underscores the need for integrated, One Health-based surveillance to monitor the emergence and spread of resistant strains in non-target environments and to assess potential cross-resistance risks to medical triazoles.

Keywords: *Aspergillus fumigatus*; azole fungicides; tebuconazole; environmental AMR; yerba mate; extractivist systems; One Health.

Palavras-chave: *Aspergillus fumigatus*; fungicidas triazóis; tebuconazol; RAM ambiental; erva-mate; sistemas extrativistas; Uma Saúde.

MONITORING AIRBORNE *ASPERGILLUS FUMIGATUS* IN BRAZILIAN SUGARCANE FIELDS: A COMPARATIVE ASSESSMENT OF AUTOMATED SPORE TRAPS / Monitoramento de *Aspergillus fumigatus* no ar em campos de cana-de-açúcar brasileiros: Uma Avaliação comparativa de armadilhas automatizadas de esporos

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ABSTRACT: *Aspergillus fumigatus*, a ubiquitous airborne fungus, is the primary causative agent of invasive aspergillosis. Effective surveillance of its environmental dispersal is critical for public health risk assessment. This study evaluated the performance of an automated, active air-sampling device (SmartAgri) against the standard passive Delta-Trap for monitoring airborne *A. fumigatus* in sugarcane fields. The two trap types were deployed concurrently in two municipalities in São Paulo state, Brazil. The automated SmartAgri collector actively sampled a defined air volume of 216 m³ per day, with spores captured on glass slides coated with double-sided tape. The passive Delta-Trap utilized proprietary qPCR-compatible adhesive seals. The adhesive substrates from each trap were aseptically transferred to Petri plates and covered with selective Dichloran Rose Bengal Chloramphenicol (DRBC) agar; plates were incubated at 48 °C for 35 hours for the selective cultivation and quantification of *A. fumigatus* colonies. Data from both collector types showed consistent patterns. A two-way ANOVA revealed significant main effects for sampling month ($p = 0.0006$) and location ($p = 0.0020$), as well as a significant month-by-location interaction ($p = 0.0001$), confirming that spore concentrations exhibited distinct temporal and spatial dynamics. The automated SmartAgri trap proved to be a viable and effective tool for this application, offering key advantages such as the ability to quantify sampled air volume, controlled aspiration, and protected sample storage. The operational SmartAgri unit will be demonstrated alongside this presentation.

Keywords: *Aspergillus fumigatus*; environmental surveillance; airborne spores; spore trap; automated monitoring; quantitative air sampling.

Palavras-chave: *Aspergillus fumigatus*; vigilância ambiental; esporos aéreos; armadilha de esporos; monitoramento automatizado; amostragem quantitativa de ar.

SURVEILLANCE AND DISTRIBUTION OF *ASPERGILLUS FUMIGATUS* IN ECOLOGICAL AND URBAN ENVIRONMENTS OF CAMPINAS, BRAZIL / Vigilância e distribuição de *Aspergillus fumigatus* em ambientes ecológicos e urbanos de Campinas, Brasil

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ABSTRACT: Environmental surveillance of *Aspergillus fumigatus* is crucial due to the emergence of azole resistance, driven by agricultural fungicide use, which compromises the treatment of invasive aspergillosis. This study aimed to investigate the distribution and azole resistance of *A. fumigatus* in ecological parks and urban environments of Campinas, Brazil. Air sampling was conducted in 15 ecological parks on four occasions (2022-2024) and in 24 urban residences by citizen volunteers (2022-2023). Isolates from the *Fumigati* section were identified by sequencing the β-tubulin gene. Antifungal susceptibility to itraconazole, voriconazole, posaconazole, and isavuconazole was determined, and resistant isolates were screened for mutations in the *cyp51A* gene. A total of 236 strains were recovered, with a significantly higher number from parks (184/15 parks) than from urban houses (52/24 houses). Azole-resistant strains were detected exclusively in park environments. The Botanical Park yielded two resistant isolates: one with an N248K mutation (resistant to isavuconazole) and another resistant to itraconazole without a known *cyp51A* mutation. Furthermore, four multi-azole-resistant strains harboring TR34/L98H/S297T/F495I and F46Y/G54R/M172V/N248T/D255E/E427K mutations were identified in three other parks. The exclusive finding of azole-resistant *A. fumigatus* in ecological parks highlights these areas as potential hotspots for resistance development and underscores their critical role in environmental surveillance programs for tracking the spread of resistant fungi.

Keywords: Invasive aspergillosis, antifungal resistance, azoles, environmental monitoring, *cyp51A* mutations.

Palavras-chave: Aspergilose invasiva, resistência antifúngica, azóis, monitoramento ambiental, mutações no *cyp51A*.