Antifungal Susceptibility of Respiratory *Aspergillus* Isolates from Canadian Hospitals: Results of the CANWARD 2013 Study.

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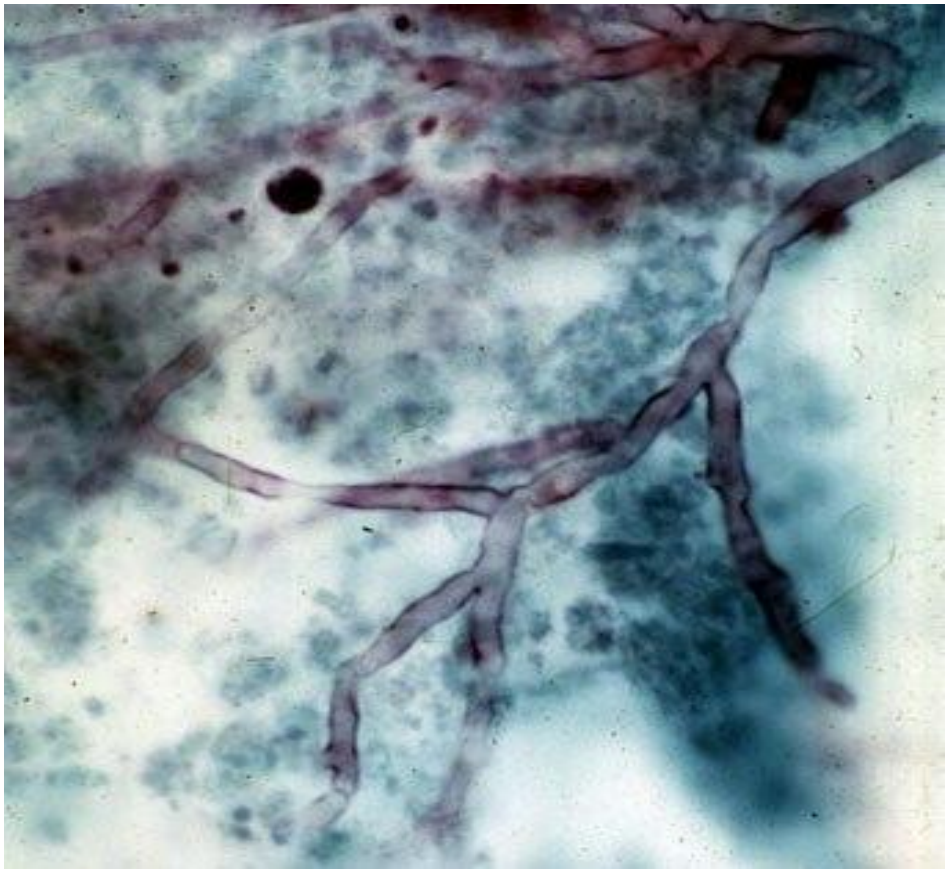
CANADIAN ANTIMICROBIAL RESISTANCE ALLIANCE CARA

Invasive Aspergillosis



Aspergillus Resistance – Current Knowledge

- *A. fumigatus* is the most prevalent species (~70%)
- *A. flavus, A. niger, A. terreus* are increasing
- Antifungal resistance in *Aspergillus* is 'rare'
- No published Canadian surveillance studies
- ID and susceptibility testing is not standard practice
- ECOFF (ECVs) values available for common species
  - Based on MIC, identify isolates that are less likely to be clinically susceptible to treatment with a specific antimicrobial agent due to acquired resistance mechanisms

Aspergillus Resistance – Current Knowledge

- Azole R in *A. fumigatus* is increasing, particularly in Europe and Asia; estimated at 3-6% globally
  - Correlates to the intensity of fungicide use in agriculture
- *de novo* selection of azole resistance on therapy is increasingly being reported in *A. fumigatus, A. flavus,* and *A. terreus*
- Intrinsic azole R in *A. calidoustus*, *A. lentulus*, and *A. pseudofisheri*
- Reduced activity of AmB against *A. flavus* and *A. terreus*
- Echinocandins and MEC challenge *in vitro* detection of R

CANWARD

- A national population-based surveillance study of pathogens and antimicrobial susceptibility in medical centres across Canada
  - Coordinated out of HSC, University of Manitoba
- Respiratory *Aspergillus* surveillance
  - Characterize the species and MIC distribution of *Aspergillus spp.*
  - 2012 to 2013
  - Central test site, University of Alberta Hospital, Edmonton

Methods – CANWARD 2012 to 2016

- Participating sites:
  - Tertiary care medical centres from 8 provinces
  - 13 clinical laboratories
- Isolate collection and inclusion:
  - *Aspergillus* isolated from clinical specimens; respiratory
  - Patients attending hospital clinics, emergency rooms, medical/surgical wards, and intensive care units
- Antifungal susceptibility testing:
  - CLSI M38, Broth microdilution guidelines

CANWARD Participating Investigators

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Dr. M. Desjardins – The Ottawa Hospital, Ottawa

Dr. M. Laverdière – Hôpital Maisonneuve-Rosemont, Montreal

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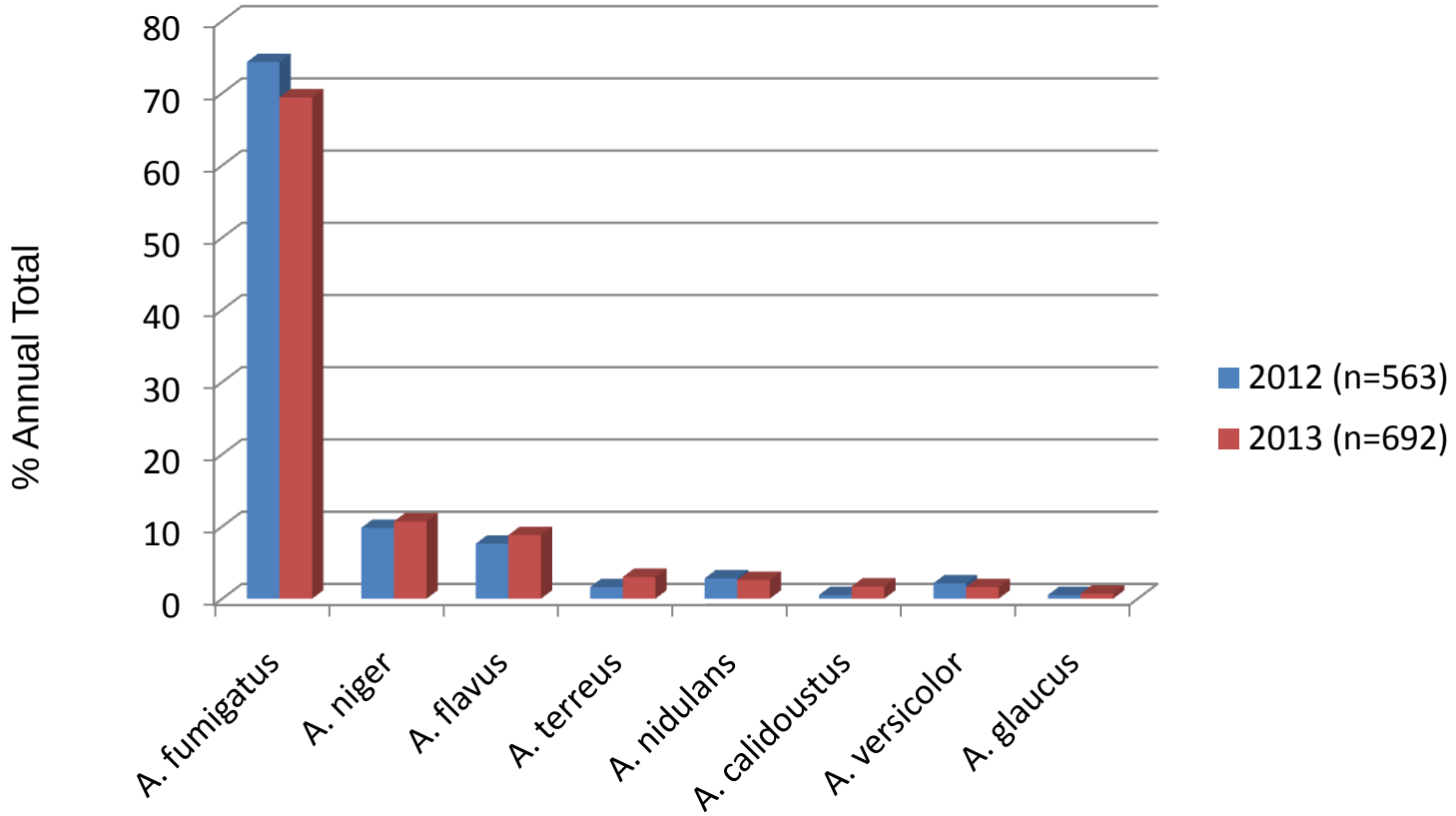
Dr. M. Goyette – CHRTR Pavillon Ste. Marie, Trois-Rivières

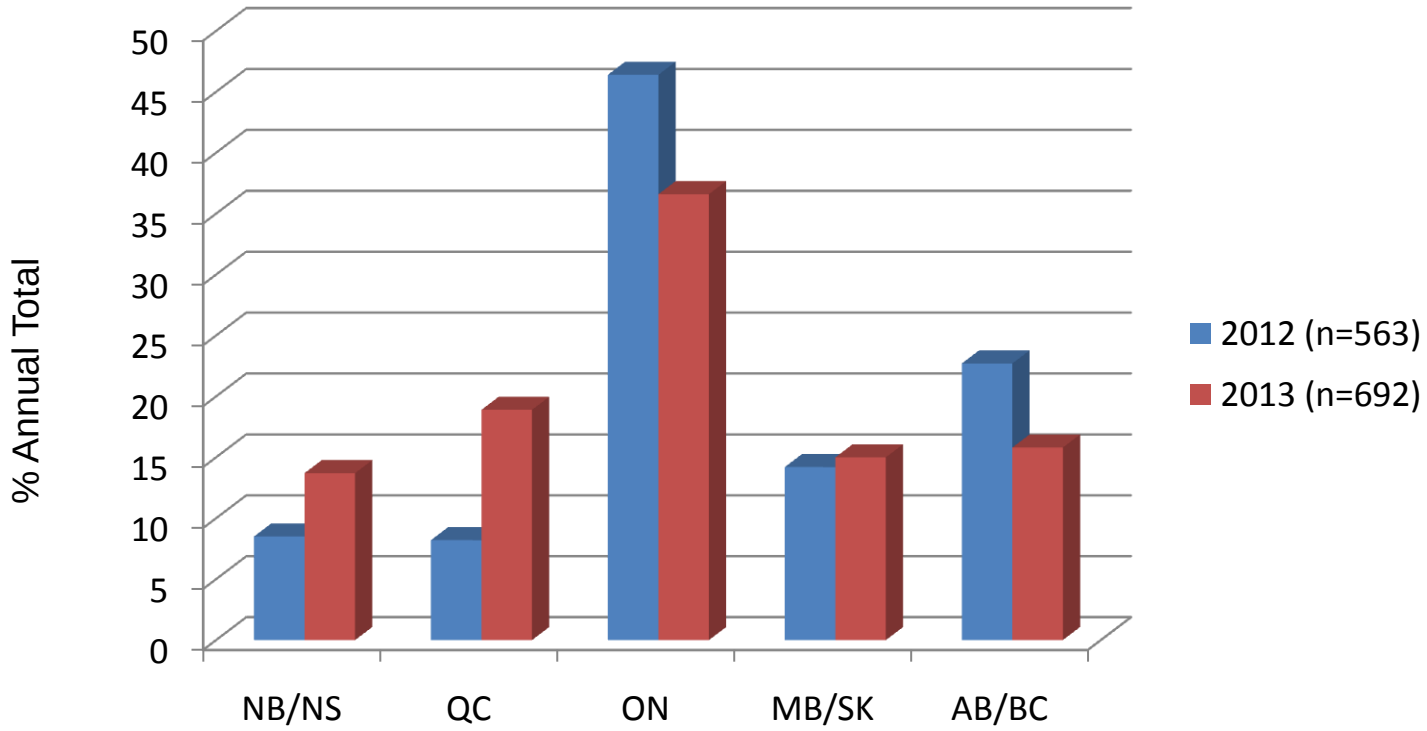
Dr. M. Kuhn – South East Regional Health Authority, Moncton

Dr. R. Davidson – Queen Elizabeth II HSC, Halifax

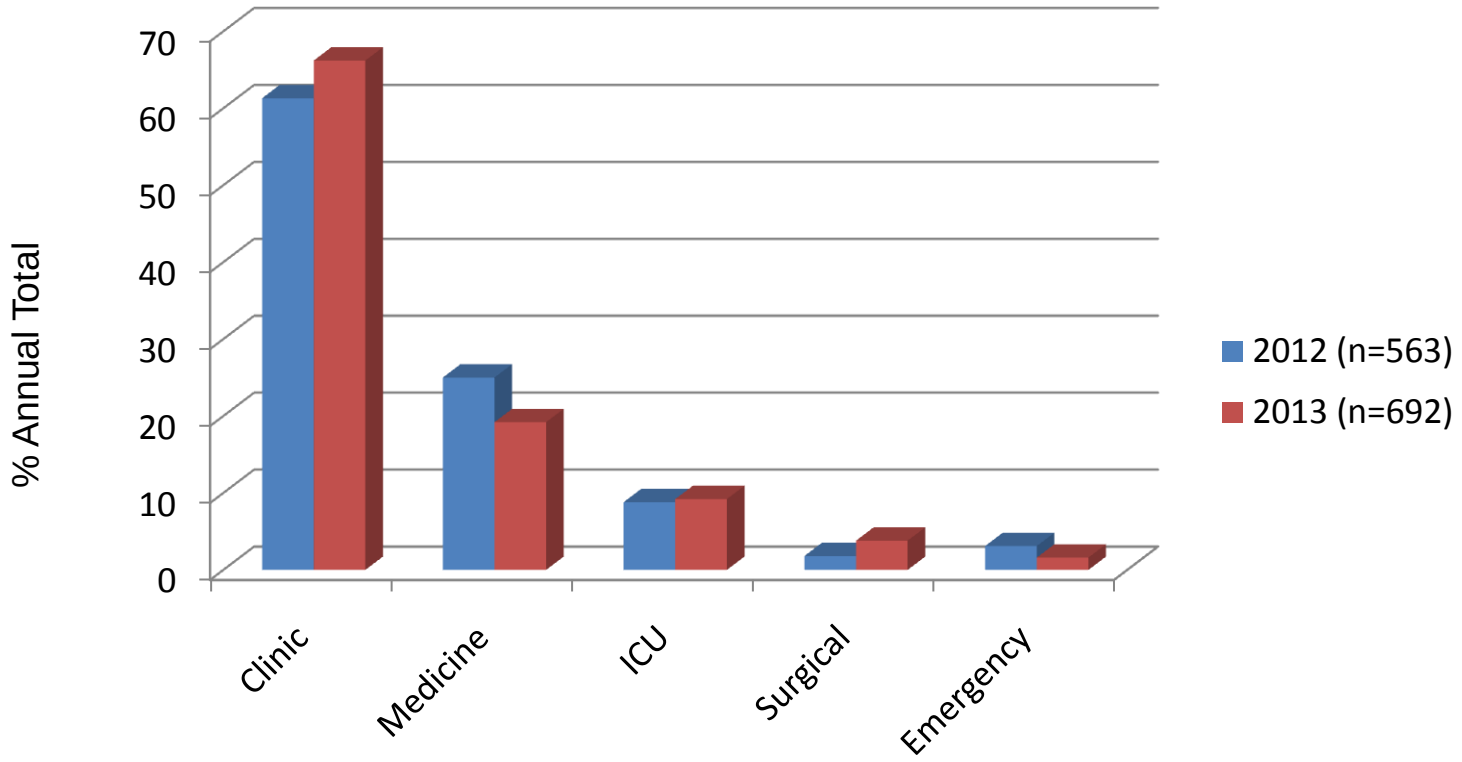
Temporal Distribution of the Most Common *Aspergillus* Species Isolated



Geographic Distribution of Surveillance Isolates



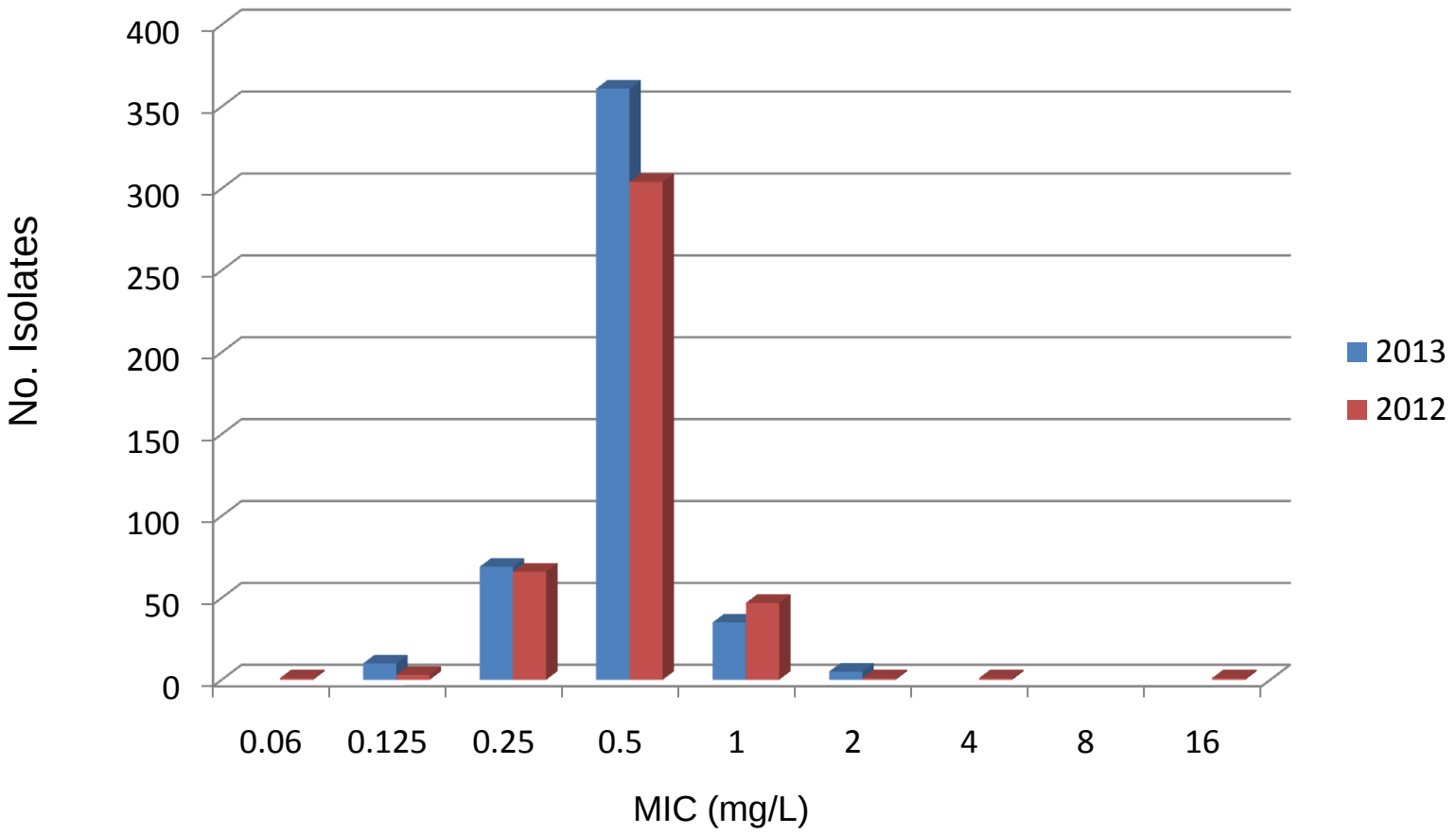
Distribution of *Aspergillus* Species Based on Patient Location



Azole MIC Distribution Against *A. fumigatus*

Agent	Year	No. Tested	Mode	MIC90	Geom Mean	ECV	% Non-wildtype (#)
VORI	2013	480	0.5	0.5	**0.479**	≤1	1 (5)
	2012	418	0.5	1	**0.486**	≤1	0.7 (3)
POSA	2013	480	0.06	0.125	**0.076**	≤0.5	0
	2012	418	0.12	0.25	**0.198**	≤0.5	0
ITRA	2013	480	0.5	0.5	**0.369**	≤1	0
	2012	418	0.5	0.5	**0.432**	≤1	0

Voriconazole MIC Distribution Against *A. fumigatus*



ECOFF: ≤1 mg/L

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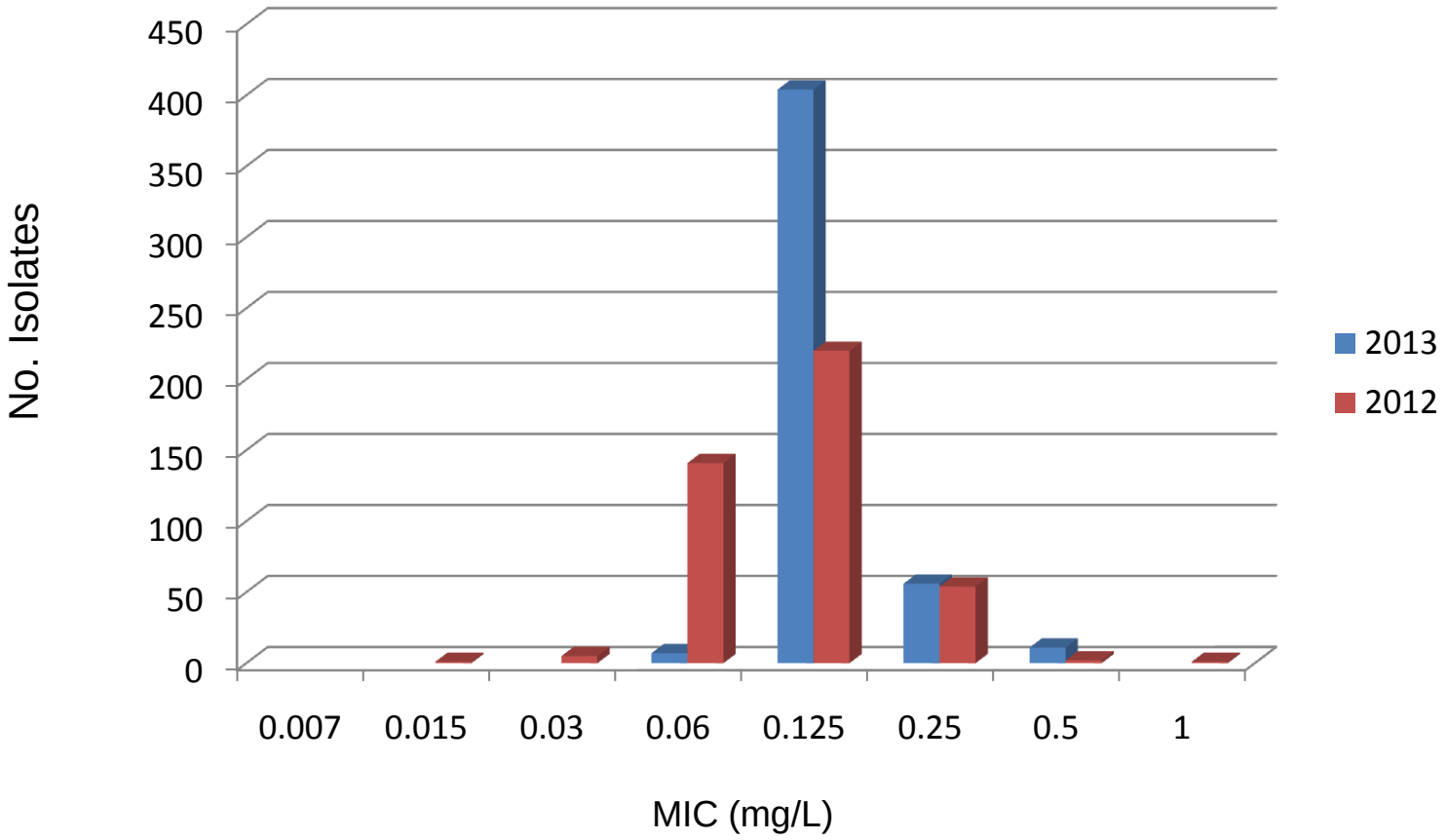
Echinocandin MIC Distribution Against *A. fumigatus*

Agent	Year	No. Tested	Mode	MIC90	Geom Mean	ECV	% Non-wildtype (#)
CASP	2013	480	0.12	0.25	**0.135**	≤0.5	0
	2012	418	0.25	0.5	**0.215**	≤0.5	0.7 (3)
MICA	2013	480	0.007	0.015	**0.008**	--	--
	2012	418	0.007	0.015	**0.008**	--	--

Caspofungin MIC Distribution Against *A. fumigatus*



ECOFF: ≤0.5 mg/L

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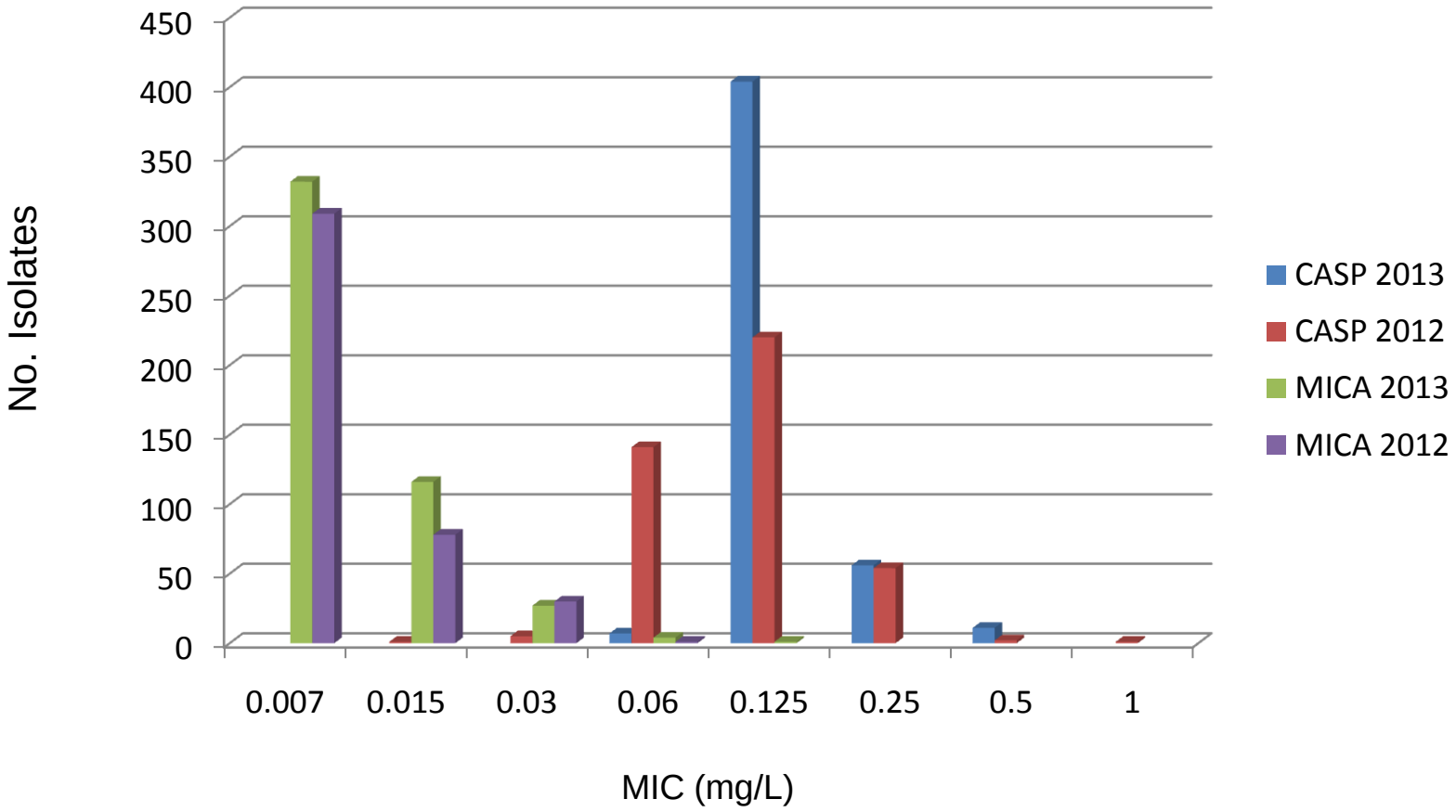
Caspofungin and Micafungin MIC Distribution Against *A. fumigatus*



Azole MIC Distribution Against *A. niger*

Agent	Year	No. Tested	Mode	MIC90	Geom Mean	ECV	% Non-wildtype (#)
VORI	2013	74	1	2	**0.614**	≤2	4.1 (3)
	2012	55	0.5	1	**0.619**	≤2	0
POSA	2013	74	0.12	0.5	**0.177**	≤0.5	4.1 (3)
	2012	55	0.25	0.5	**0.212**	≤0.5	1.8 (1)
ITRA	2013	74	0.5	1	**0.769**	≤2	6.8 (5)
	2012	55	1	2	**0.617**	≤2	1.7 (1)

Echinocandin MIC Distribution Against *A. niger*

Agent	Year	No. Tested	Mode	MIC90	Geom Mean	ECV	% Non-wildtype (#)
CASP	2013	74	0.12	0.12	**0.119**	≤0.25	0
	2012	55	0.12	0.25	**0.117**	≤0.25	1.7 (1)
MICA	2013	74	0.007	0.007	0.007	--	--
	2012	55	0.007	0.007	0.007	--	--

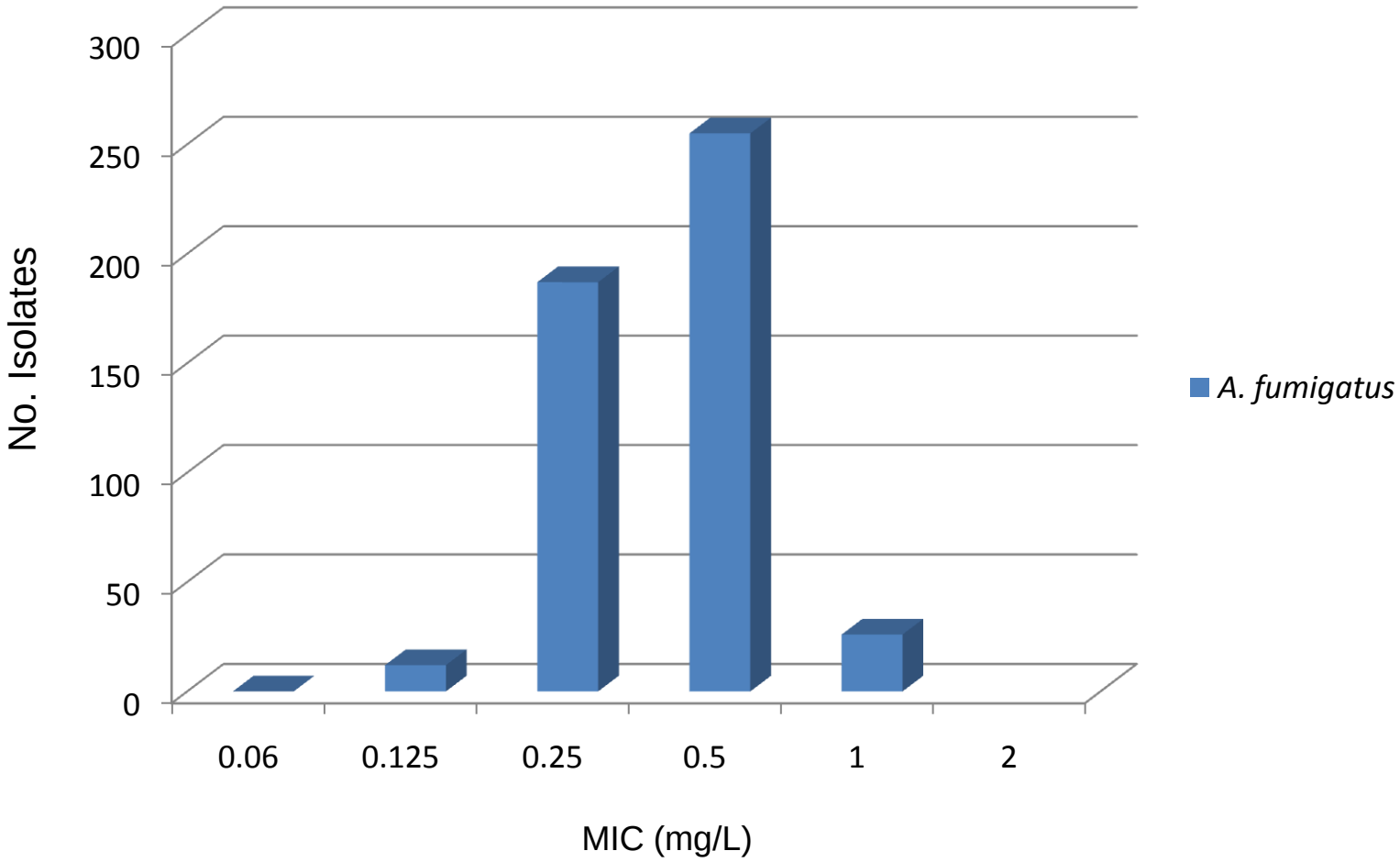
Azole MIC Distribution Against *A. flavus*

Agent	Year	No. Tested	Mode	MIC90	Geom Mean	ECV	% Non-wildtype (#)
VORI	2013	61	1	2	**1.050**	≤2	4.9 (3)
	2012	43	1	2	**1.033**	≤2	4.7 (2)
POSA	2013	61	0.25	1	**0.173**	≤1	0
	2012	43	0.25	0.5	**0.178**	≤1	0
ITRA	2013	61	0.5	1	**0.368**	≤1	0
	2012	43	0.5	1	**0.436**	≤1	0

Echinocandin MIC Distribution Against *A. flavus*

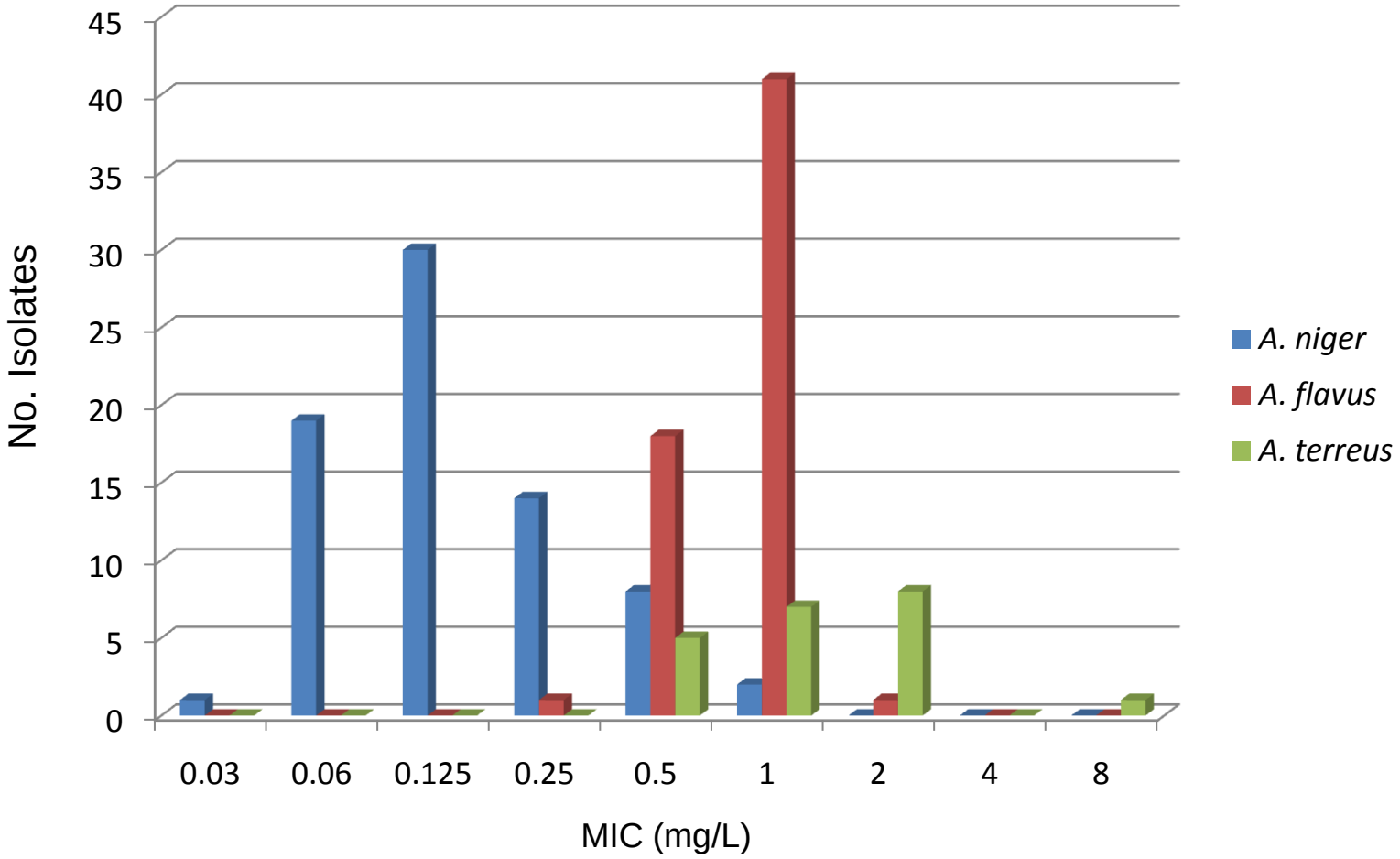
Agent	Year	No. Tested	Mode	MIC90	Geom Mean	ECV	% Non-wildtype (#)
CASP	2013	61	0.12	0.25	**0.129**	≤0.25	4.9 (3)
	2012	43	0.12	0.25	**0.174**	≤0.25	6.7 (3)
MICA	2013	61	0.007	0.03	**0.010**	--	--
	2012	43	0.007	0.03	**0.008**	--	--

Amphotericin B MIC Distribution Against *A. fumigatus*



ECOFF: ≤2 mg/L

Amphotericin B MIC Distribution Against Uncommon *Aspergillus* Species



ECOFF: ≤2 mg/L for *A. niger, A. flavus*; ≤4 mg/L *A. terreus*

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A. calidoustus

- Intrinsically resistant to azoles
- ~50% resistant to caspofungin
- Possible emergence linked to azole prophylaxis and lung transplant patients

CANWARD

- 2013 - 12 isolates from 5 laboratory sites
  - Azole MICs >16 mg/L
  - Caspofungin MECs >4 mg/L for 5 isolates
- 2012 – 4 isolates submitted

Egli, Fuller, et al. 2012. *Transplant*. 2012; 94(4):403.

CANWARD - *Aspergillus* Resistance Rates

2013	Overall Resistance (%)					
Species	VORI	POSA	ITRA	CASPO	MICA	AMB
A. fumigatus	1	0	0	0	(0)	0
A. flavus	4.9	0	0	4.9	(0)	0
A. niger	4.1	4.1	6.8	0	(0)	0

- Antifungal activities of azoles and echinocandins are high against the most common species of *Aspergillus* in Canada
- Overall azole resistance (all isolates) was 4.5%
- *A. flavus* (and *A. calidoustus*) azole resistance will be important for continued surveillance

Summary

- Species prevalence indicates that the epidemiology has not significantly changed
- MIC results confirm that activity of available antifungals remains excellent
- ECOFFs discriminate non-wildtype isolates against azoles, amphotericin B, and caspofungin
- Reference method and ECOFFs provide tool for surveillance and detection of emergent acquired resistance

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