Antifungal Susceptibility of *Aspergillus* Isolates from the Respiratory Tract of Patients in Canadian Hospitals: Results of the CANWARD 2016 Study.

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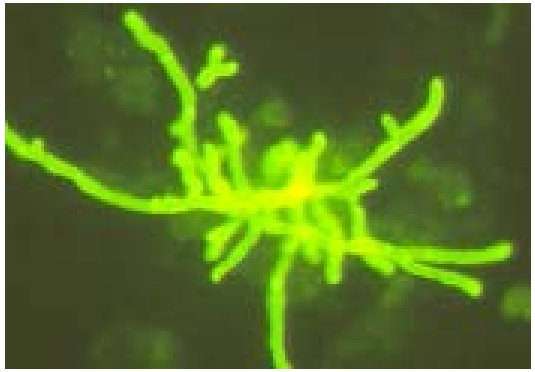
COI Disclosures

Research Grants

- Astellas
- Merck
- Pfizer

Aspergillus Disease in Canada

- 2nd most common cause of invasive fungal infection
  - Predominantly invasive pulmonary disease
  - Estimated 1.6 cases of IA per 100,000 population
  - 5 to 13% incidence in HSCT and haematological malignancy patients and 25% attributable mortality



- Non-invasive pulmonary aspergillosis
  - 381.8 cases per 100,000 population

- *A. fumigatus >>> A. flavus / A. niger*

Dufresne et al. EJCMID.2017;36:987-992. Haider. AMMI-CACMID 2015. Haider, et al. CJIDMM. 2014;25(1):17-23.

Aspergillus Antifungal Susceptibility Testing

- Species ID and susceptibility testing is not routine
  - Recent improvements in MS-ID technology and CLSI standards have reduced challenges for clinical laboratories
- Epidemiological cutoff values (ECV) available for common species (microbiological breakpoints)
  - CLSI M59 2nd edition, M61 1st edition
  - Distinguish wild-type MICs from abnormally elevated MICs, indicative of acquired resistance
  - ECVs have no correlation to clinical response to therapy but, in the absence of clinical breakpoints, are critical for antifungal resistance surveillance

Aspergillus Epidemiology and Resistance

- Increasing reports of azole resistance in *A. fumigatus*
  - 3 to 30% in Europe, Asia, and Middle East
  - Environmental association (intensity of agricultural fungicide use)
  - Not associated with prolonged therapeutic exposure to azoles
- Increases in azole resistant *A. flavus* and *A. terreus*
- Intrinsic azole resistance in *A. calidoustus*, *A. lentulus, and A. pseudofisheri*
- Standardized surveillance needs driven by limited understanding of resistance implications and treatment options

Resendiz Sharpe et al. Med Mycol. 2018;56:S83-S92
Hagiwara et al. Front Micro. 2016;7:

CANWARD

- A national population-based surveillance study of pathogens and antimicrobial susceptibility in hospitals across Canada
  - Coordinated out of Health Sciences Centre, University of Manitoba
- *Aspergillus* surveillance
  - Characterize species and MIC distribution of *Aspergillus spp.* from respiratory specimens
  - Determine the rate of azole resistance
- Participating sites:
  - 15 clinical laboratories at tertiary care hospitals from 8 provinces
  - Isolates collected from patients admitted to hospital clinics, emergency rooms, medical/surgical wards, and intensive care units
  - Coordinated out of University of Alberta, Edmonton

CANWARD Participating Investigators

D. Roscoe – Vancouver Hospital, Vancouver
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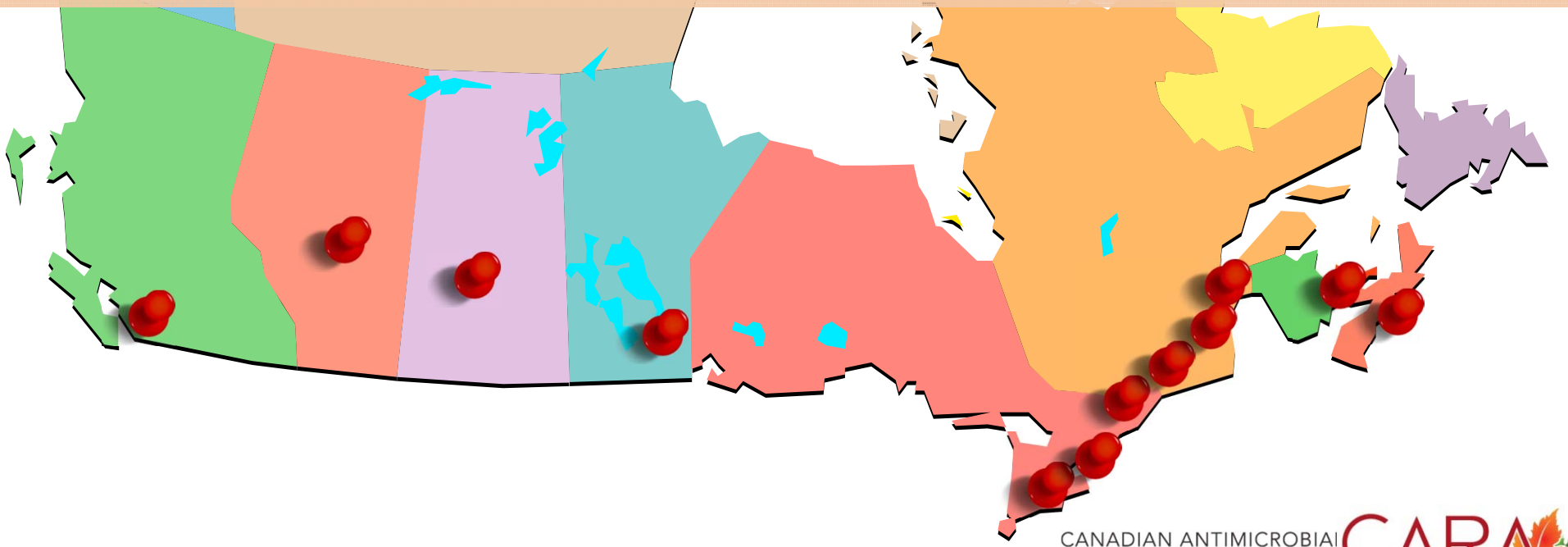

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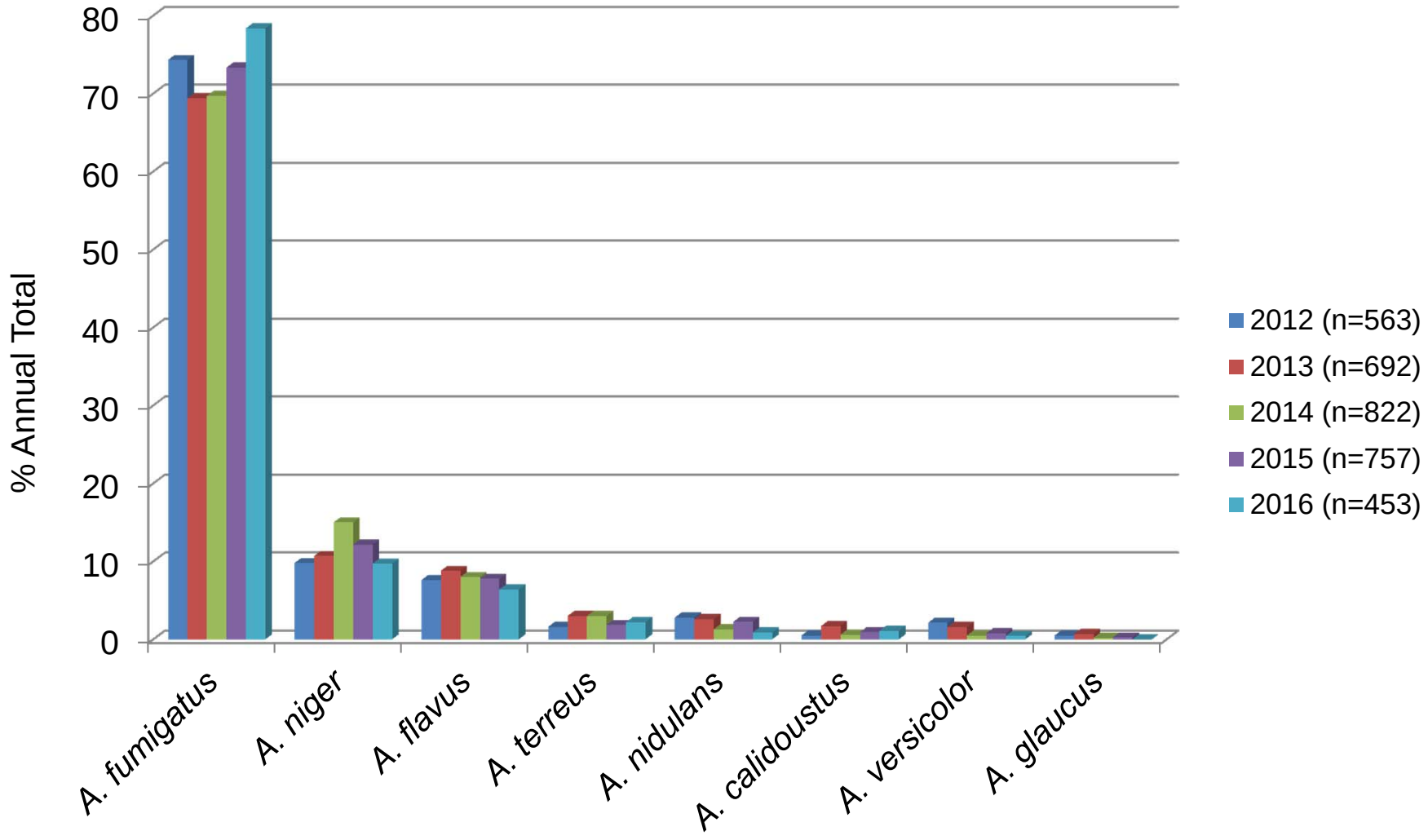
2016 Patient Demographics

- 453 respiratory tract isolates of *Aspergillus spp.*

Patient Characteristics	No. (%)
Mean age	55.1
<18 years	35 (7.7)
18 – 65 years	231 (51.0)
>65 years	187 (41.3)
Female	217 (47.9)
Male	236 (52.1)

Distribution of *Aspergillus* Species Isolated from Respiratory Specimens



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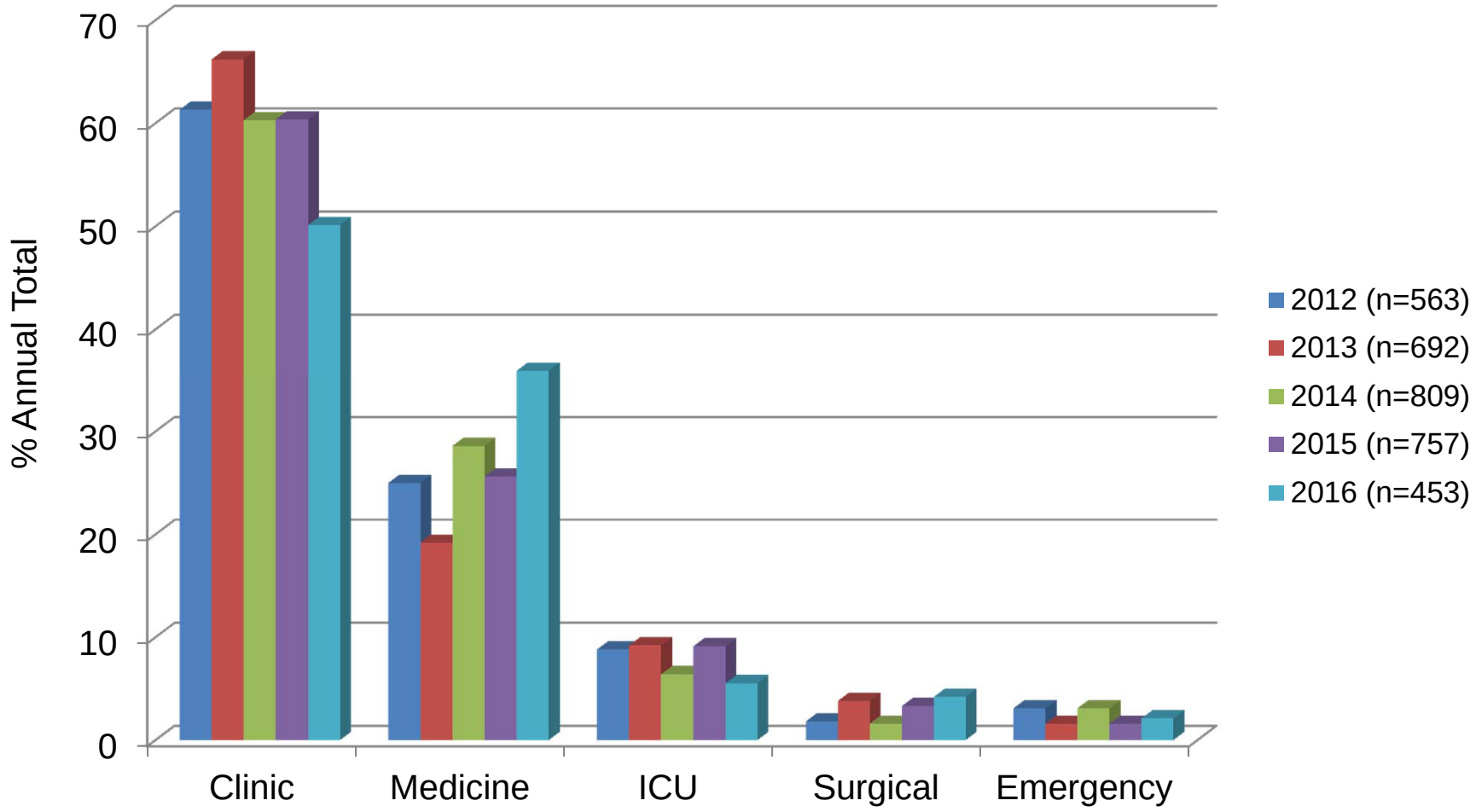
Distribution of *Aspergillus* Species Based on Patient Location in Healthcare Setting



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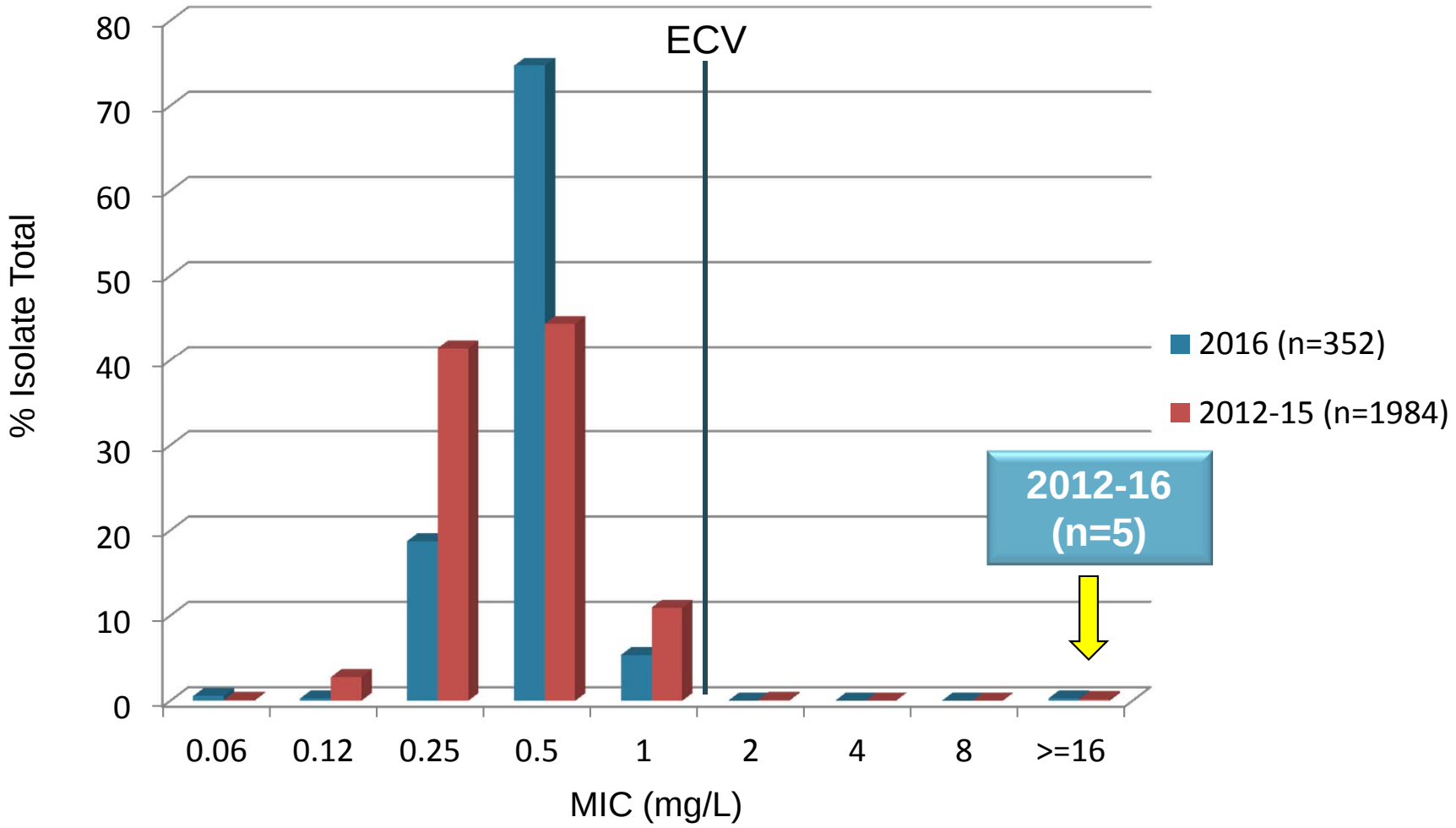
Respiratory Specimen Distribution

Year	Location	No. Isolates	% Sputum	% BAL or BW	% ETT
2016	Clinic	227	54	30	9
	Medicine	163	64	32	3
	ICU	25	28	48	24
	Surgical	19	37	63	0

Year	Location	No. Isolates	% Sputum	% BAL or BW	% ETT
2012-15	Clinic	1594	62	30	5
	Medicine	681	47	45	4
	ICU	236	23	50	22
	Surgical	76	38	41	13

Itraconazole MIC Distribution Against *A. fumigatus*



MIC >4 mg/L infers *cyp51A* mutation

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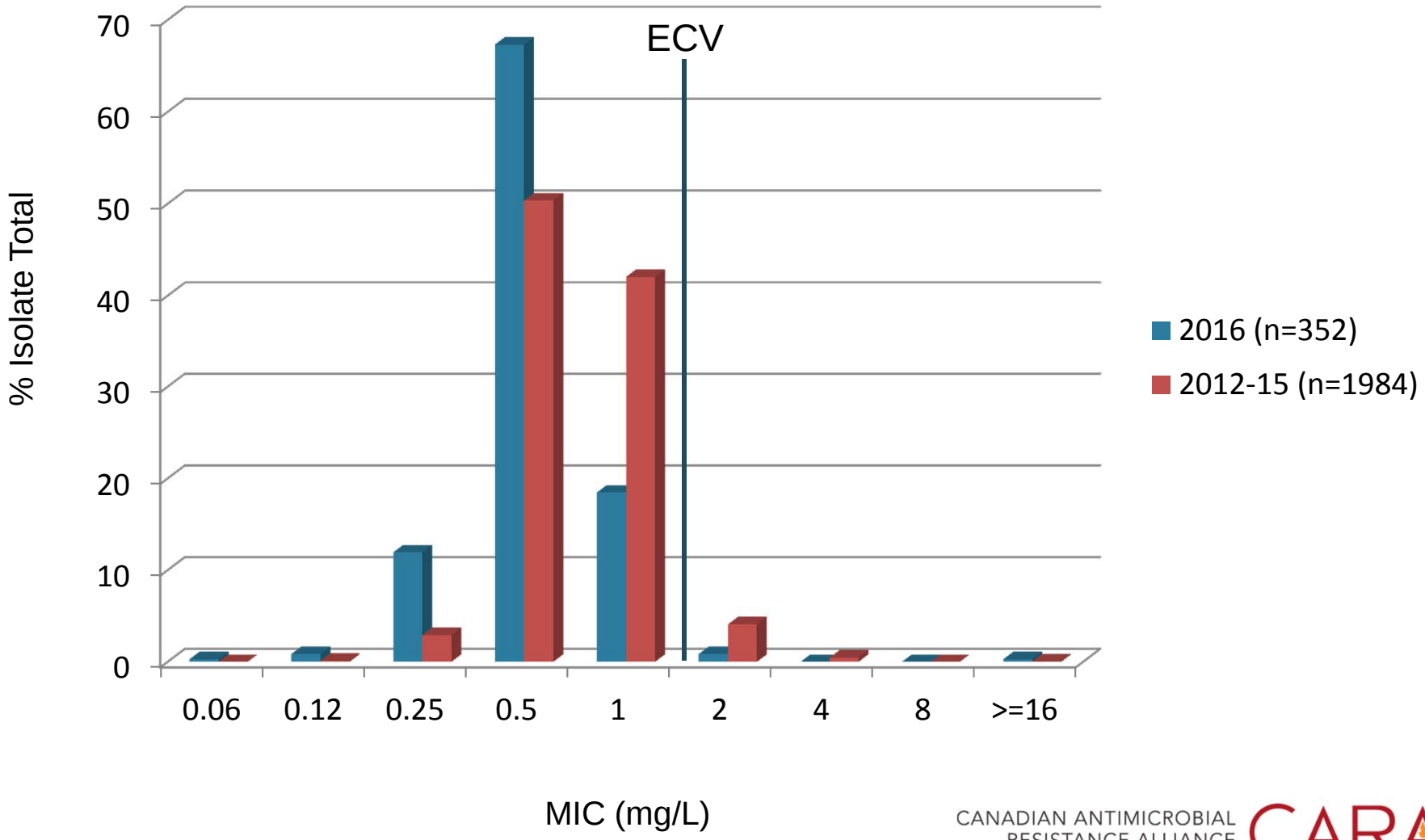
Voriconazole MIC Distribution Against *A. fumigatus*



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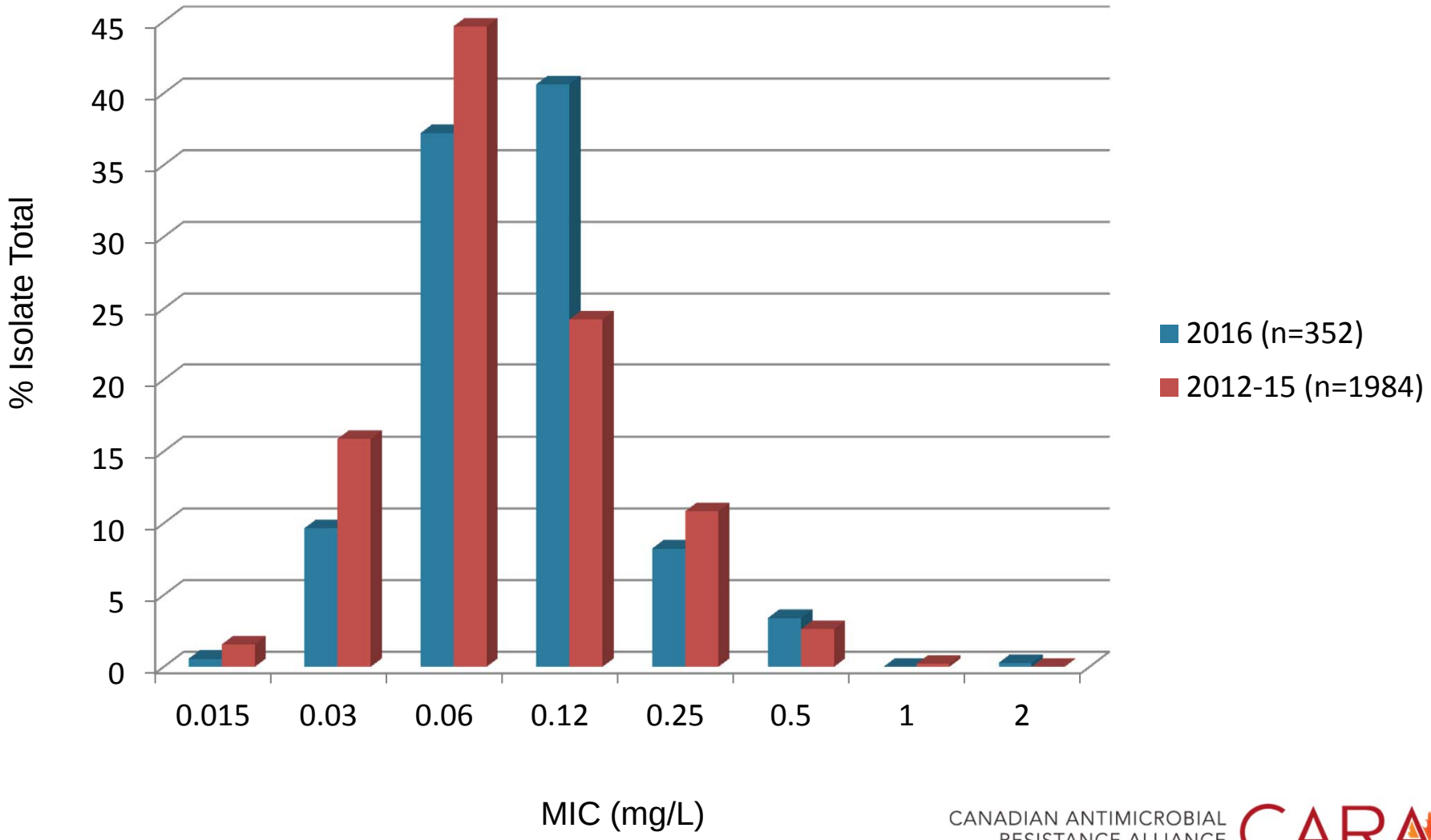
Posaconazole MIC Distribution Against *A. fumigatus*



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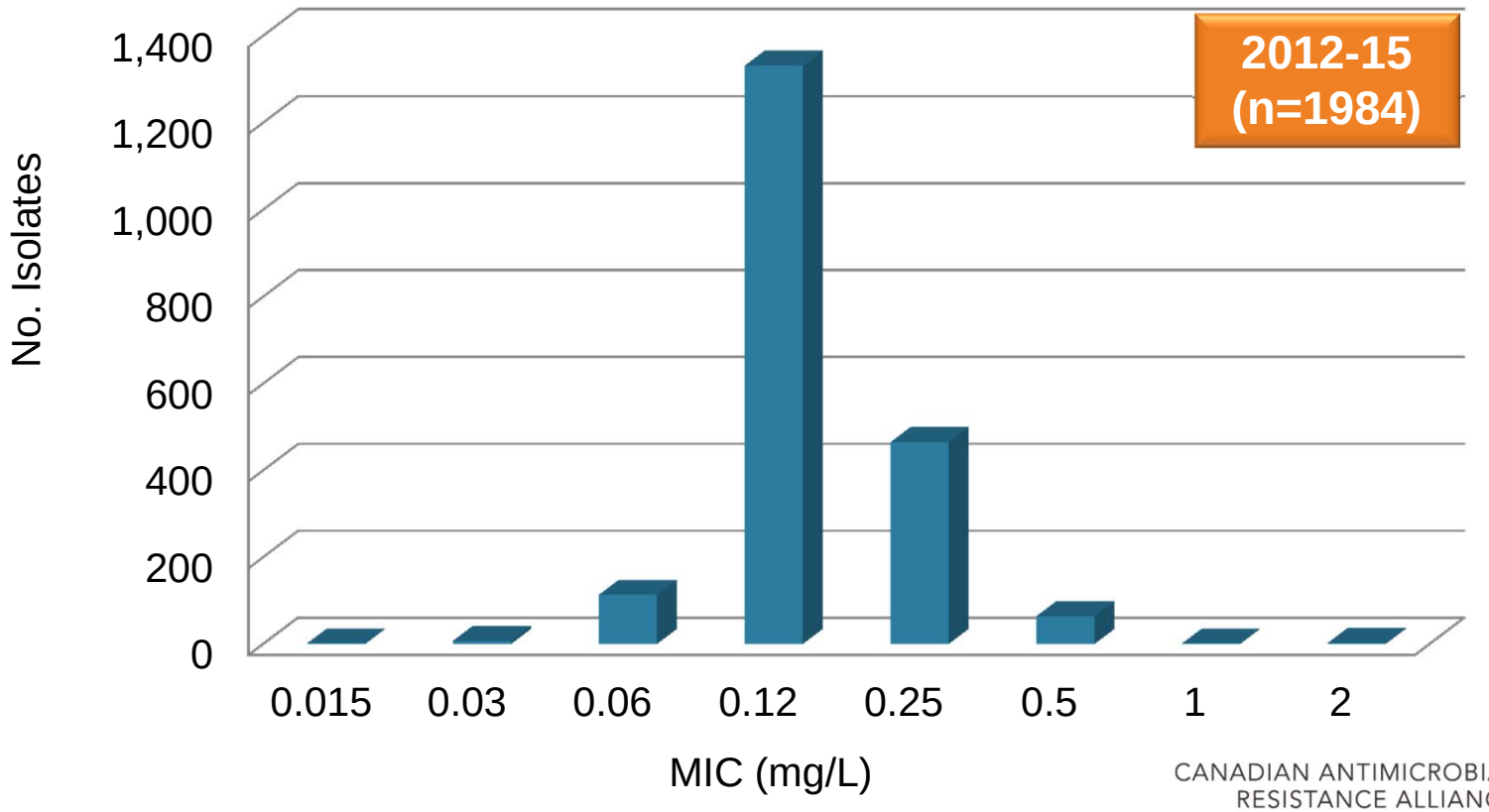
Azole Resistance in *A. fumigatus;* 2012-16

- 5 isolates of 2336 with ITRA MIC >4 mg/L
- Independent of year and participating centre
- Patient locations include 2 Clinic, 2 Medicine, and 1 ICU
- 3 of 5 had Voriconazole MICs > 1mg/L (ECV)
- *cyp51A* sequence mutations TBD

Caspofungin MIC Distribution Against *A. fumigatus*

Year	No. Tested	Mode	MIC_{90}	ECV	% Non-wildtype (#)
2016	355	0.125	0.25	≤0.5	0



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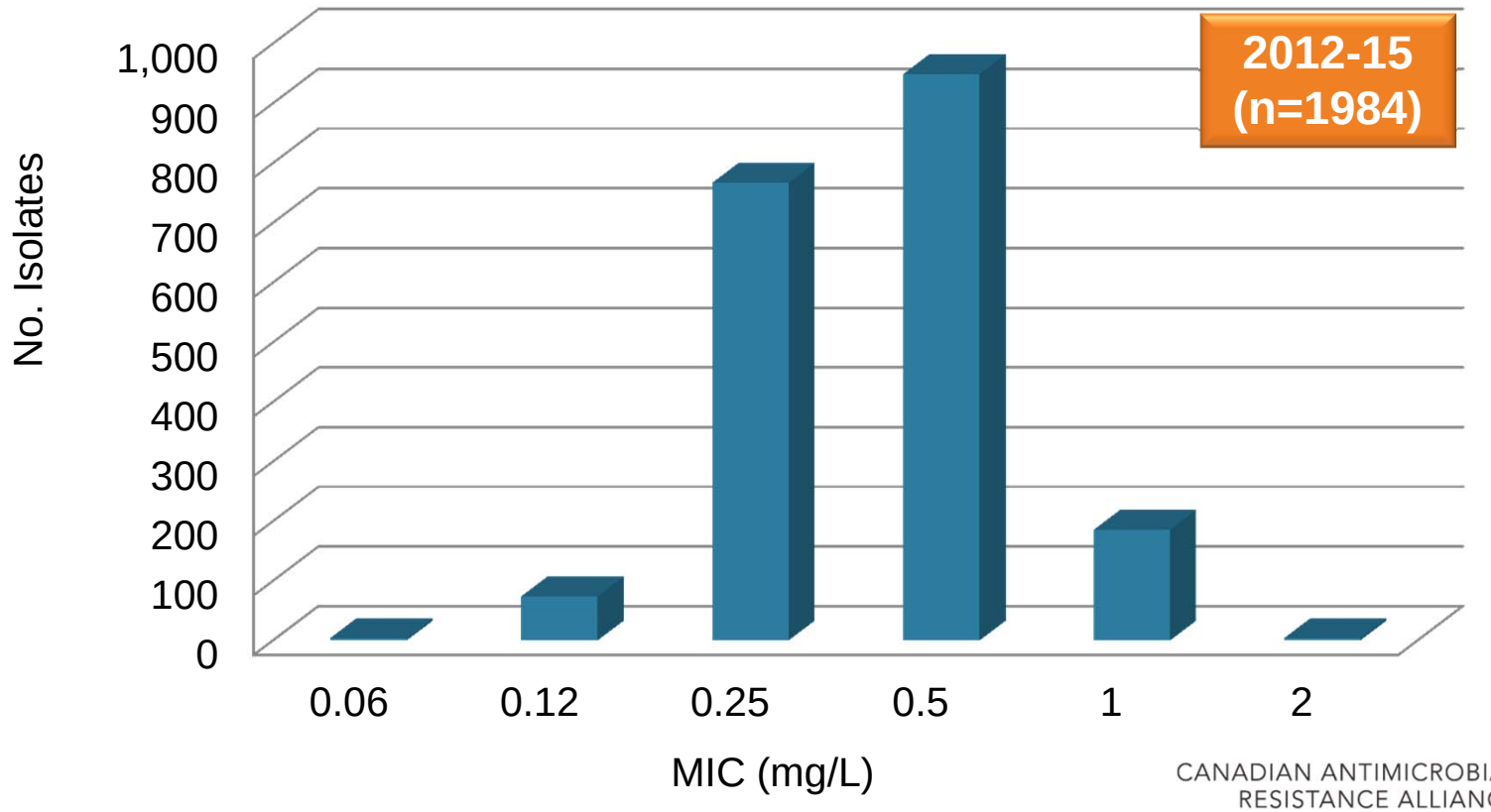
AmB MIC Distribution Against *A. fumigatus*

Year	No. Tested	Mode	MIC_{90}	ECV	% Non-wildtype (#)
2016	355	0.5	0.5	≤2	0



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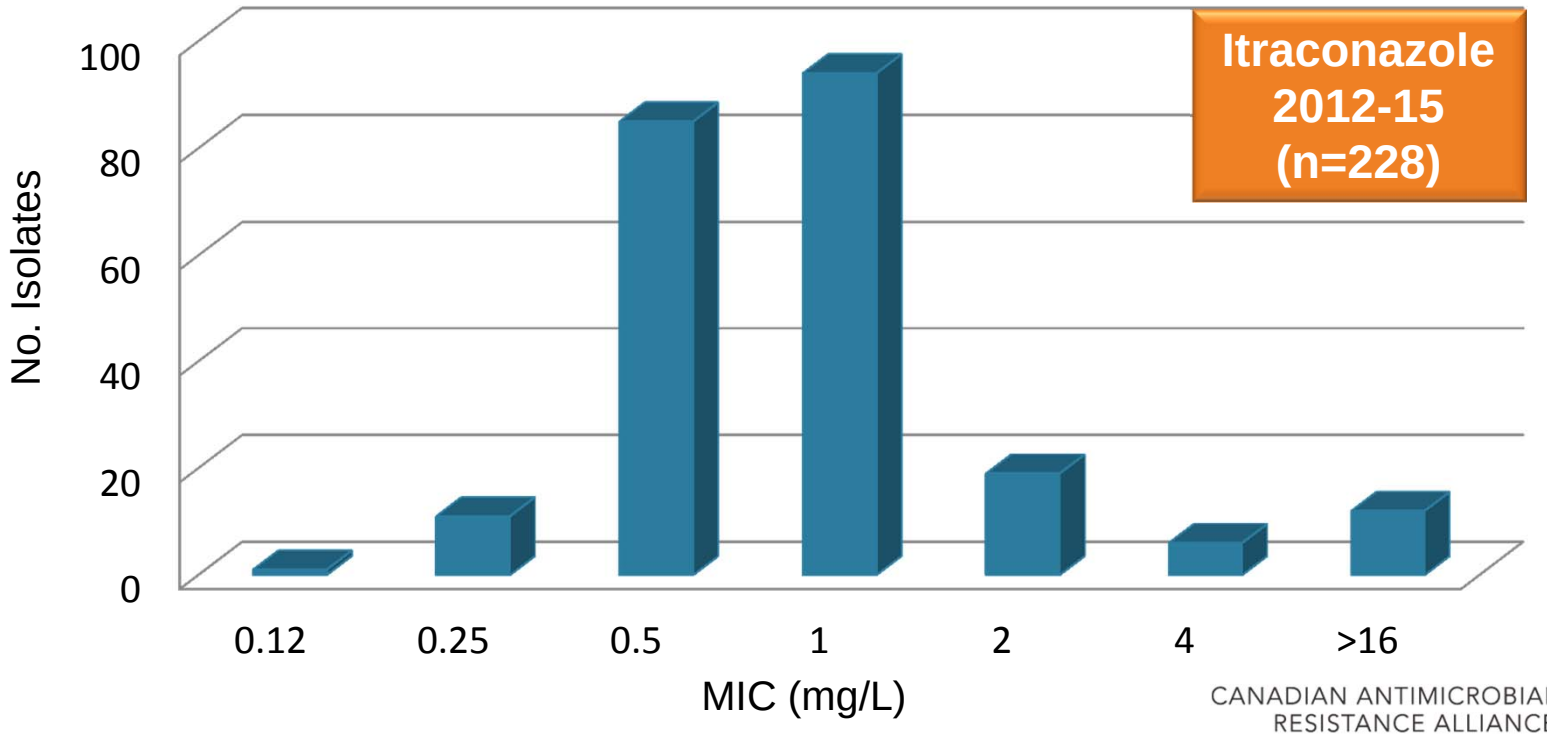
Azole MIC Distribution Against *A.* section *Nigri*

Agent	Year	No. Tested	Mode	MIC_{90}	ECV	% Non-wildtype (#)
ITRA	2016	44	1	16	≤4	29.5 (13)
VORI	2016	44	1	4	≤2	11.4 (5)
POSA	2016	44	0.12	0.5	≤2	0



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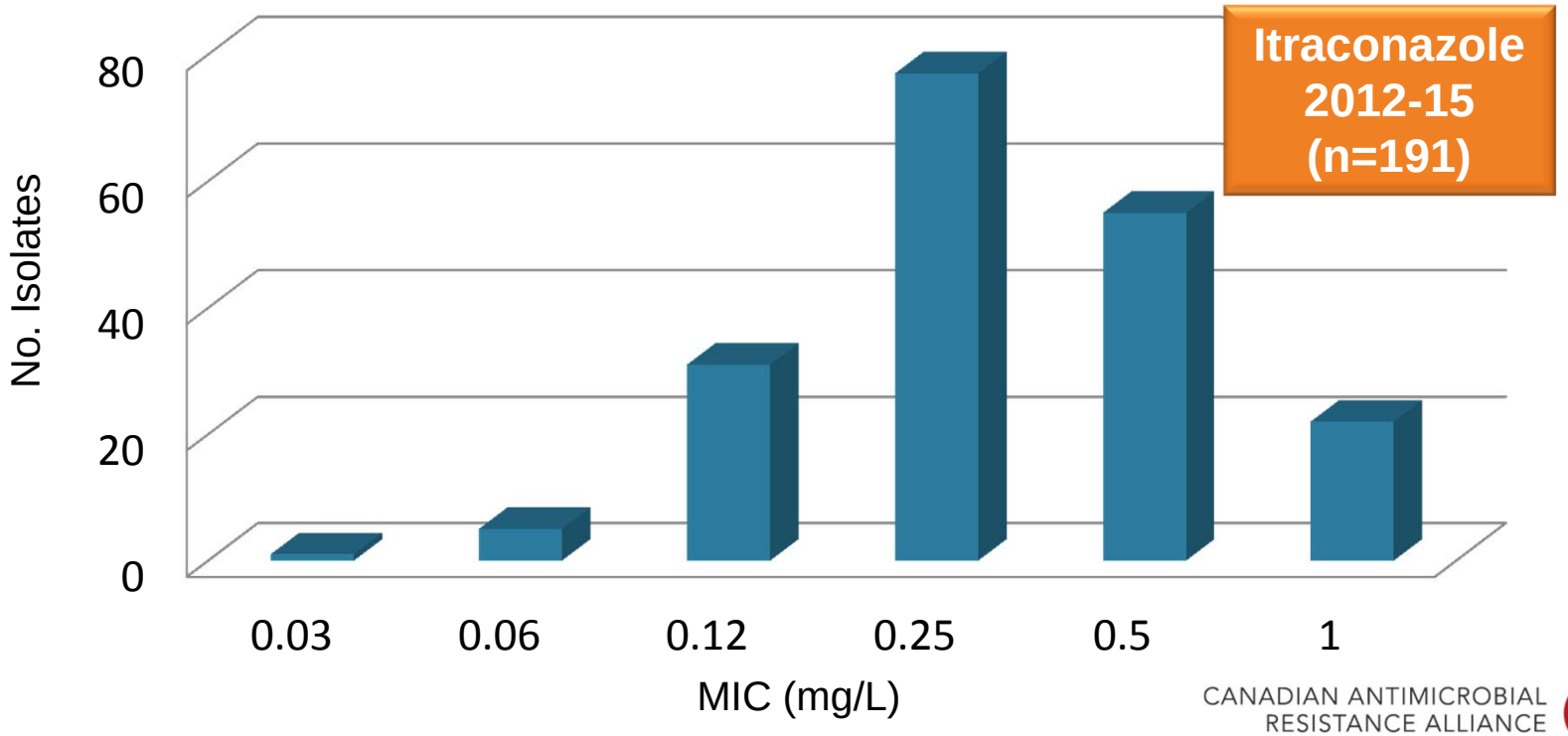
Azole MIC Distribution Against *A. flavus*

Agent	Year	No. Tested	Mode	MIC_{90}	ECV	% Non-wildtype (#)
ITRA	2016	28	0.5	0.5	≤1	0
VORI	2016	28	1	2	≤2	0
POSA	2016	28	0.12	0.5	≤0.5	0



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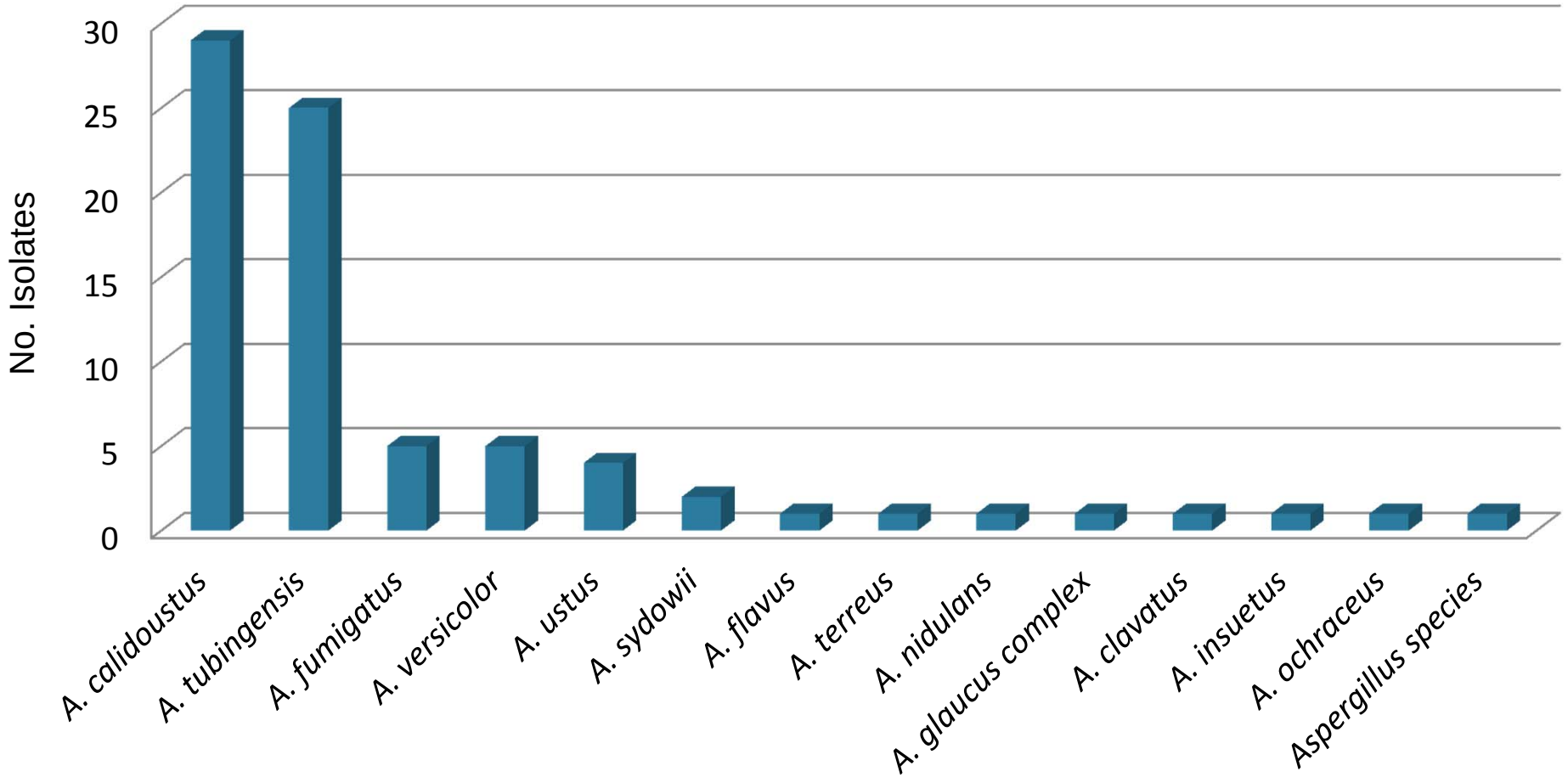
Caspofungin MIC Distributions

Agent	Year	No. Tested	Mode	MIC_{90}	ECV	% Non-wildtype (#)
A. Section *Nigri*	2016	46	0.12	0.12	≤0.25	0
	2012-15	228	0.12	0.12	≤0.25	0
A. flavus	2016	28	0.12	0.25	≤0.5	0
	2012-15	191	0.12	0.25	≤0.5	0

Isolates with Itraconazole MIC>16 mg/L (2012-16)



A. calidoustus

- *Aspergillus* section *Usti*
- Intrinsically resistant to azoles
- ~50% resistant to caspofungin
- Possible emergence linked to azole prophylaxis and lung transplant patients
- CANWARD 2012-16
  - 31 isolates collected
  - 7th most common overall (4.1% of non-*A. fumigatus*)
  - 22 from bronchial specimens
  - 18 from clinic patients and 7 from medicine patients

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

A. tubingensis

- *Aspergillus* section *Nigri*
  - Includes *A. nigri sensu stricto*
- Variable resistance to azoles has been reported
- Caspofungin MIC_{90} = 0.12 mg/L
- Bronchial colonization, invasive aspergillosis, otomycosis
  - MALDI and sequence ID efforts are rewriting our understanding of this species and human disease
- CANWARD 2012-16
  - Itraconazole resistant species are sequence-confirmed
  - 25 isolates collected
  - 10% of *A.* section *Nigri* isolates and 3.4% of non-*A. fumigatus* species
  - 14 from bronchoscopy specimens
  - 17 from clinic patients and 5 from medicine patients

Gautier, et al. *Med Mycol*. 2016; 54:459.

CANWARD - *Aspergillus* 2016

- 453 *Aspergillus* isolates from respiratory specimens
- *A. fumigatus, A.* section *Nigri, A. flavus*, *A. terreus*, and *A. calidoustus* represented 78.4%, 10.2%, 6.4%, 2.2%, and 1.1% of the population
- *A. fumigatus* isolates were recovered primarily from
  - Sputa (60.0%) and bronchoscopy (31%) specimens
  - Clinic outpatients (47.0%) and inpatients admitted to Medicine (38.5%) and Critical care (5.6%) services
- *A. fumigatus* exhibited WT MIC values against the azoles, CASP and AmB
  - 1 isolate exhibited azole resistance with an ITRA MIC >16 mg/L
- 13 presumptive *A. tubingensis* were detected with ITRA MICs >16 mg/L
- Five *A. calidoustus* isolates exhibited azole resistance (ITRA $\geq$4 mg/L)

CANWARD – *Aspergillus* Resistance in Respiratory Specimens

2012-16	**% Resistance (no.)**		
Species (n)	ITRA	CASP	AMB
A. fumigatus (2339)	0.2 (5)	0.1 (3)	0
A. Section *Nigri* (274)	9.2 (25)	0.4 (1)	0
A. flavus (221)	0.5 (1)	0	0
A. calidoustus (31)	93.6 (29)	--	--

- Azole resistance in *A. fumigatus* is extremely rare in Canadian patients
- Significant azole resistance in *A.* section *Nigri* (ie. *A. tubingensis*)
  - MS-ID for moulds is not common; conventional ID = *A. niger*
- In total, 78 (2.5%) isolates resistant to azoles (ITRA >16 mg/L)