9° congresso nazionale
Genova, 22-23 giugno 2017
Starhotels President
D.I.T.M.O.
Diagnostica e Terapia delle Micosi Opportunistiche

Fungicidi in agricoltura

Anna M. Tortorano
Università degli Studi di Milano

FUNGICIDI in uso in agricoltura

Classificazione armonizzata (Commissione Comunità Europea 11/12/2006)

Inorganici (F1): zolfo, rame

Carbammati e ditiocarbammati (F2)

Benzimidazoli (F3)

Imidazoli e triazoli (F4) es. difenoconazolo, epoxiconazolo, fenbuconazolo, flusilazolo, exaconazolo, propiconazolo, tebuconazolo, tetraconazolo

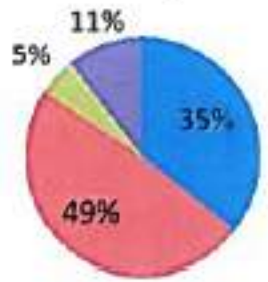
Morfoline (F5)

Altri (F6): azotoalifatici, ammidici, anilidici, aromatici, dicarbossimidici, dinitroanilinici, dinitrofenolici, fosforganici, ossazolici, fenilpirrolici, ftalimmidici, pirimidinici, chinolinici, chinonici, strobilurinici

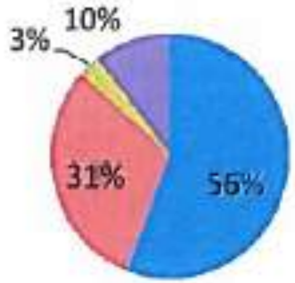
Volume of active ingredients sold in EU

ECPA Statistical Review 2013

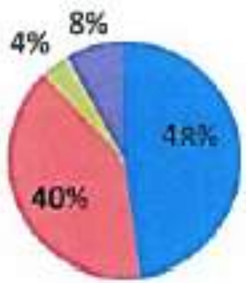
Total Eu 28



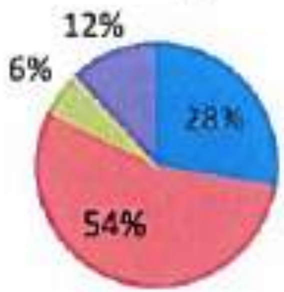
Northern zone



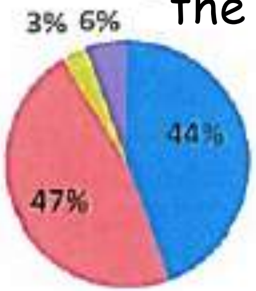
Central zone



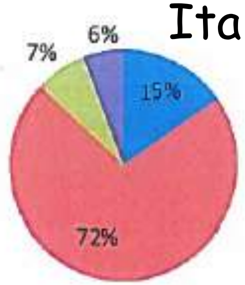
Southern zone



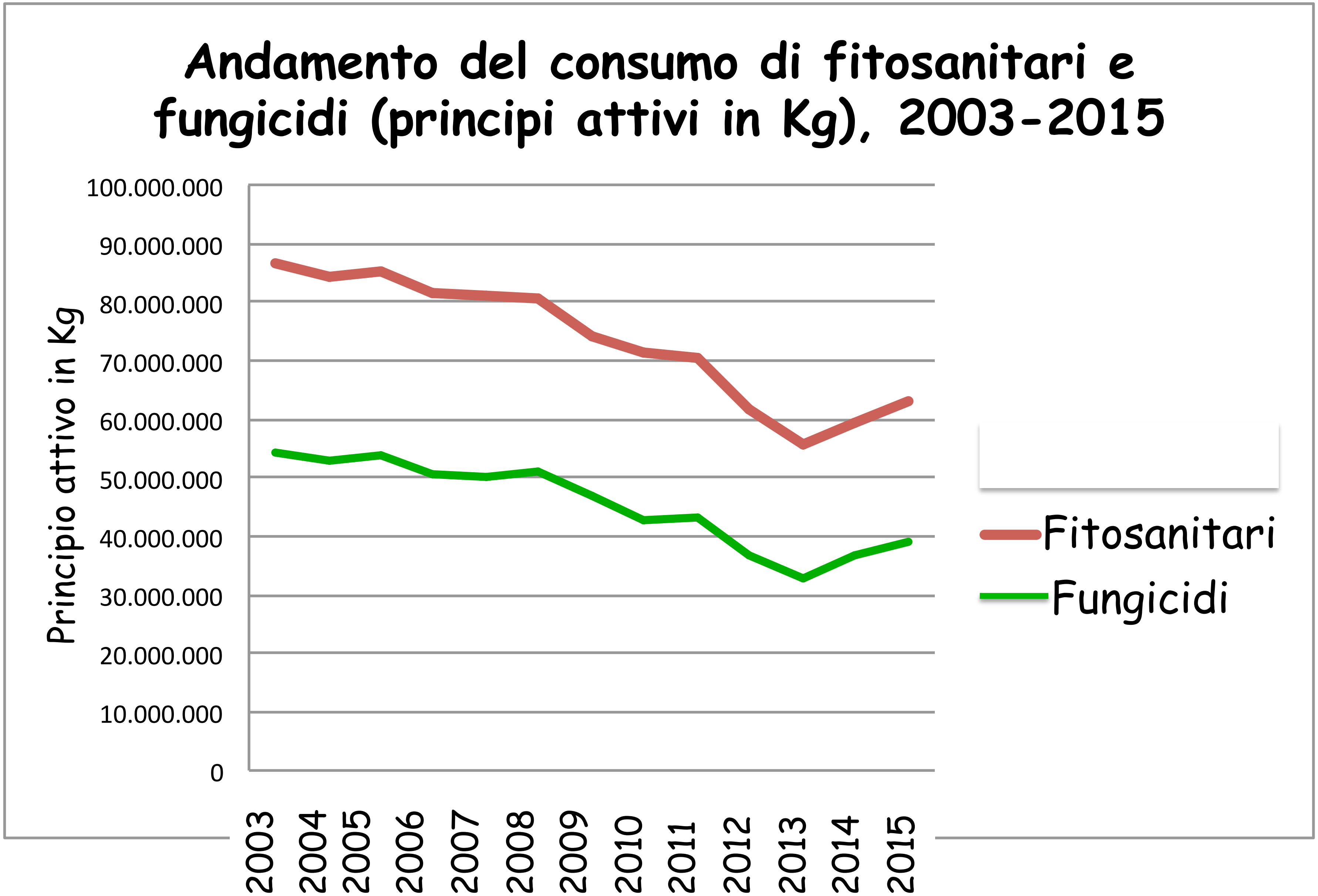
the Netherlands

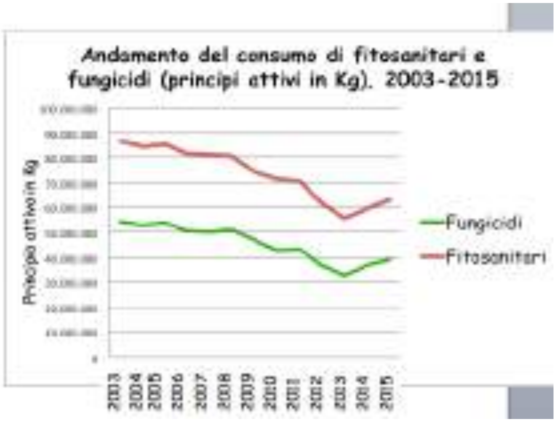


Italy



ITALIA


Andamento del consumo di fitosanitari e fungicidi (principi attivi in Kg), 2003-2015
Principio attivo in Kg
100.000.000
90.000.000
80.000.000
70.000.000
60.000.000
50.000.000
40.000.000
30.000.000
20.000.000
10.000.000
0
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
Fitosanitari
Fungicidi



2003-2015
-50% Insetticidi
-30% Erbicidi
-30% Fungicidi

2003-2015
-40% Zolfo
-30% Rame
-23% Solforganici

+133% Triazoli

FUNGICIDI AZOLICI

Vantaggi

- costo relativamente contenuto
- ampio spettro di attività
- persistenza nell'ambiente
  (uso prevenzione e trattamento)

Utilizzo prodotti fitosanitari in differenti coltivazioni

dati ISTAT

	Fungicidi*	Triazoli*
Mais (2007)	No	
Avena (2003)	No	
Orzo (2003)	No	
Ulivo (2011)	Sì 55%	No
Vite (2015)	Sì 93%	Sì 0,12%
Patata (2013)	Sì 71%	Sì 0,21%
Frumento tenero (2008)	Sì 46%	Sì 15,6%
Frumento duro (2008)	Sì 35%	Sì 9,3%
Pomodoro (2012,2014,2015)	Sì 79-88%	Sì 0.3-0.9%

Largo impiego dei triazoli anche per

- Barbabietola da zucchero
- Orticole
- Fruttiferi (pomacee e drupacee)

* % della quantità di fungicidi impiegata nei trattamenti fitosanitari

Numero di applicazioni di fungicidi per stagione

- Cereali: 0-4
- Colza: 0-2
- Patate: 5-10
- Mele: 8-15

Lisa Nistrup Jorgensen, TIMM 2013

Septoria tritici

Fusarium lycopersici

Fusarium graminearum

Fusarium Head blight of Wheat
Photo Dr. Gary Bergstrom, Cornell University

Infezione del pomodoro da *Peronospora*

Ticchiolatura del melo
Venturia inaequalis/ Spilocea pomi

Trichoderma viride infects tulip roots

Plasmopora viticola

Aspergillus carbonarius

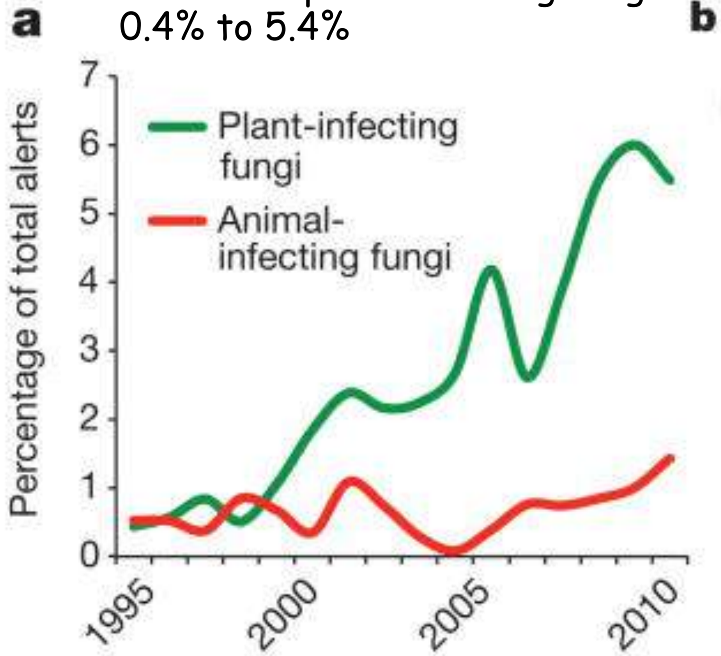
Foto da: Blackthorn Agricultural stock image; Cornell University; Growertalks; Belli G. Elementi di patologia vegetale. Piccin

Emerging fungal threats to animals, plants and ecosystem health

MC Fisher et al Nature 2012

Emerging infectious diseases caused by fungi

Trend for plant infecting fungi
0.4% to 5.4%



Fungal diseases occurred worldwide

Perchè trattare con fungicidi ?

I funghi possono causare

- diminuzione del rendimento delle coltivazioni del 5-50%
- diminuzione della qualità dei prodotti e della possibilità di conservazione
- formazione di micotossine

Emerging fungal disease threaten food security

Crop *Host species*	2009/2010 harvest (million tonnes)	Calories per 100g flour (un-cooked)	Disease/Pathogen and variation in % losses	Loss of food* for *x* million over 1 year, given diet of 2,000 calories per day
Rice	701 harvest but 476* milled for food	325	***Magnaporthe oryzae*** 10-35%	212 to 742
Wheat	679 harvest but 432* for food	341	***Puccinia graminis*** 10-70%	202 to 1,413
Maize	820 harvest but 271* for food	355	***Ustilago maydis*** 2-20%	26 to 262
Potato	333* harvest but for food	357	***Phytophthora infestans*** 5-78%	81 to 1,270
Soybean	232 harvest but 148* for food	372	***Phakospora pachyrhizi*** 10-80%	75 to 600

Total: Could feed 596 (9%) - 4,287 (61%) million mouths *per annum*

M. Fisher TIMM 2013

Direzione Generale Ambiente Commissione UE (2006 e 2009)

TETRACONAZOLO e FLUSILAZOLO
potenziali effetti nocivi sul sistema endocrino

limitazioni nell'uso
eventuale fuoriuscita dal mercato dei fitofarmaci

COLDIRETTI

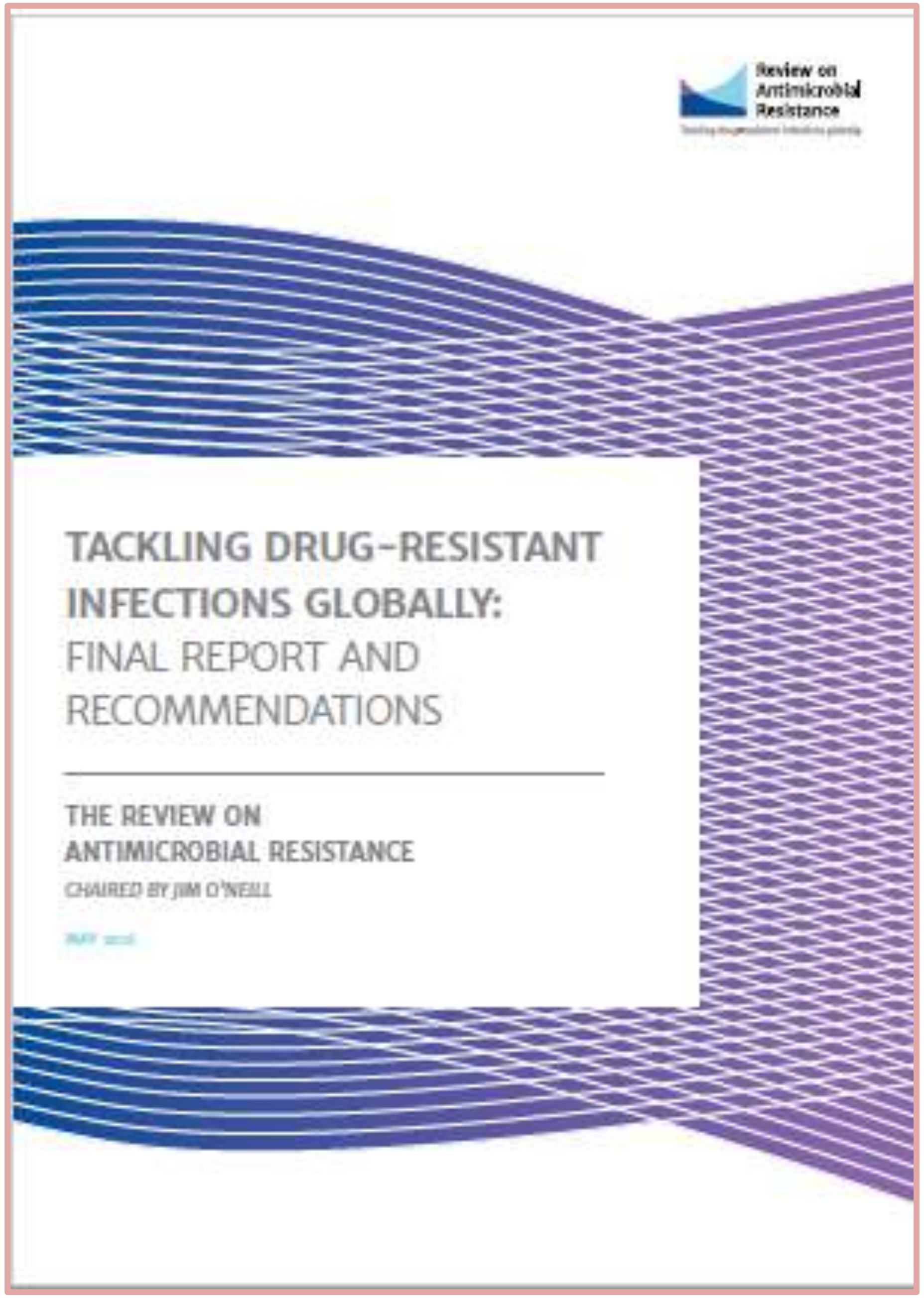
IL RUOLO DEI FITOFARMACI A BASE DI AZOLI NELLA DIFESA FITOSANITARIA DI ALCUNE COLTURE DELL'AGRICOLTURA ITALIANA ED EUROPEA.

ottobre 2014

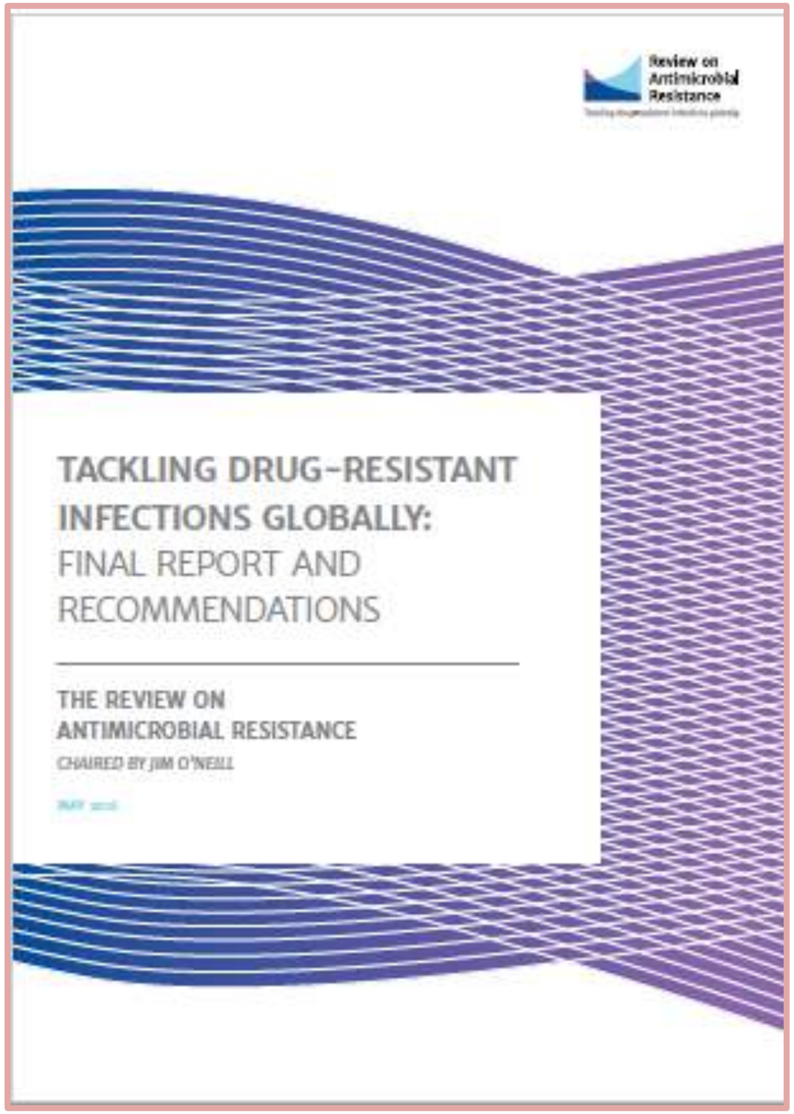
Fuoriuscita dal mercato dei fitofarmaci a base di azoli

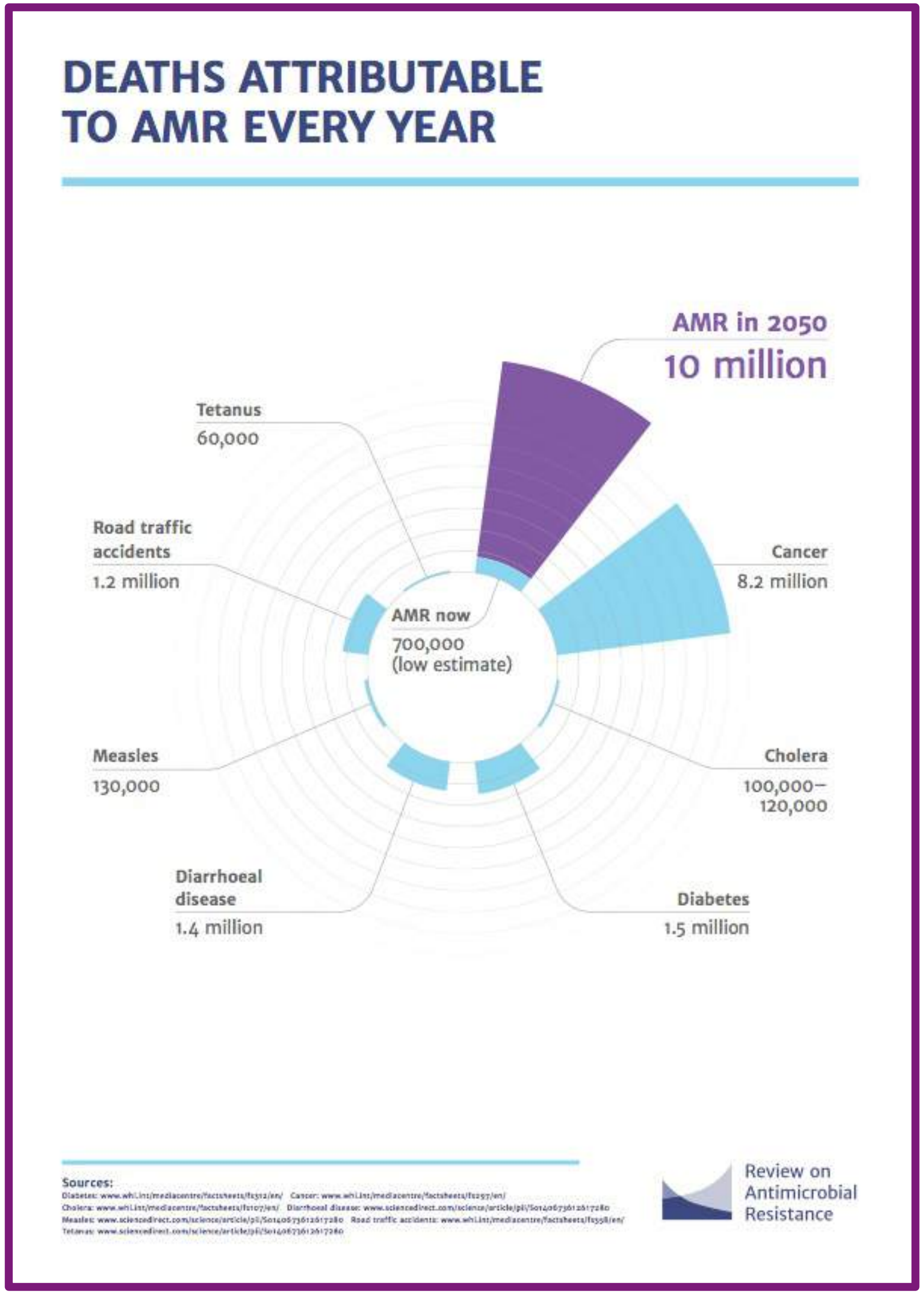
- svantaggio concorrenziale per agricoltori europei
- diminuzione delle rese e della disponibilità totale della produzione
- peggioramento della qualità del prodotto con implicazioni di natura commerciale (caratteristiche organolettiche e aspetto) e sulla salute umana e zootecnica (micotossine)
- aumento dei prezzi e della volatilità dei prezzi

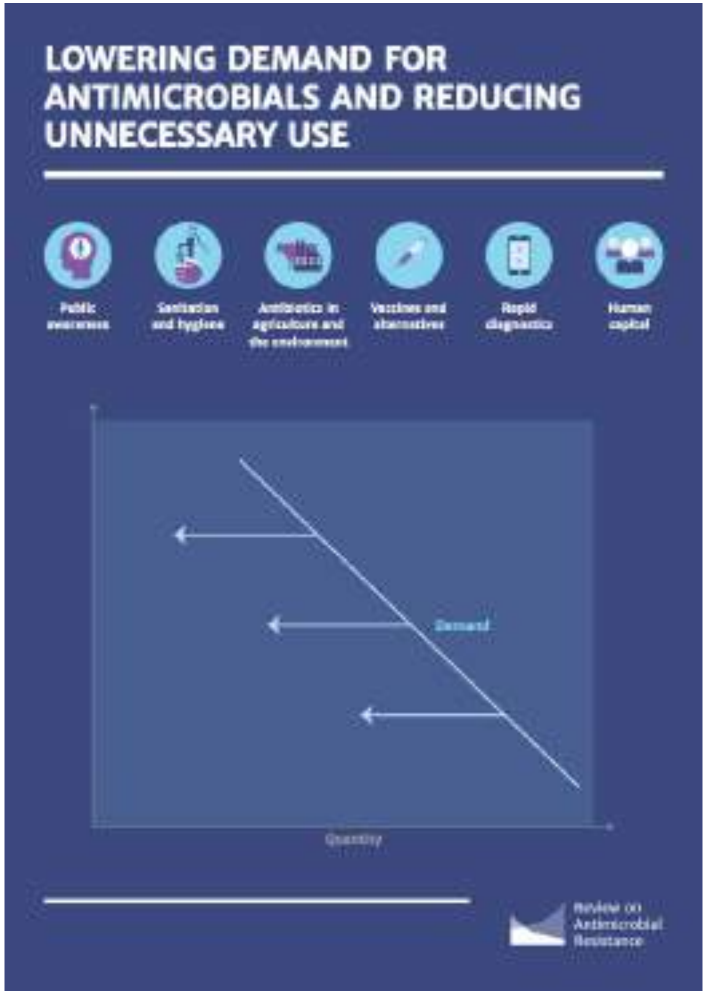
….e la resistenza ??

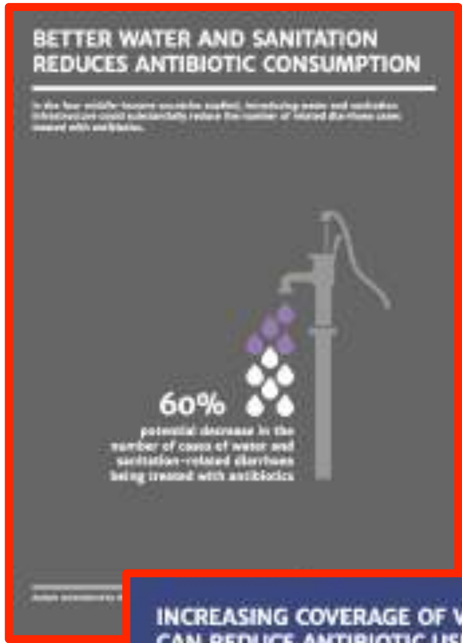


In 2014 the UK Prime Minister D.Cameron commissionated the independent review on antimicrobial resistance chaired by macroeconimist Jim O'Neil

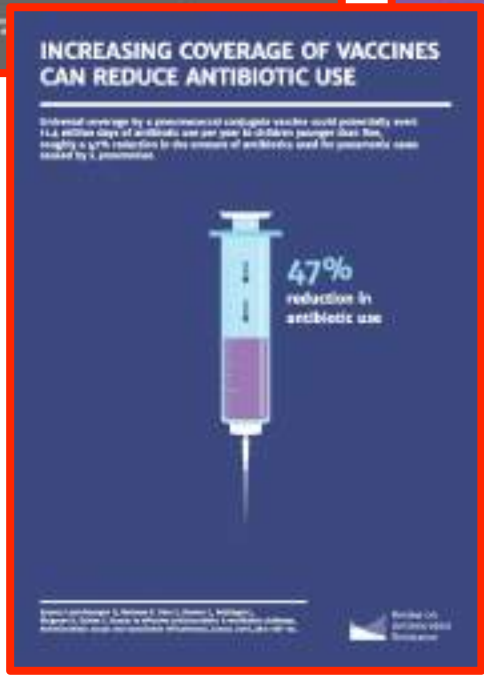

Review on Antimicrobial Resistance
TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY:
FINAL REPORT AND RECOMMENDATIONS
THE REVIEW ON ANTIMICROBIAL RESISTANCE
CHAIRED BY JIM O'NEILL


DEATHS ATTRIBUTABLE TO AMR EVERY YEAR
AMR in 2050
10 million
Tetanus
60,000
Road traffic accidents
1.2 million
Cancer
8.2 million
AMR now
700,000
(low estimate)
Measles
130,000
Cholera
100,000–120,000
Diarrhoeal disease
1.4 million
Diabetes
1.5 million
Sources:
Review on Antimicrobial Resistance

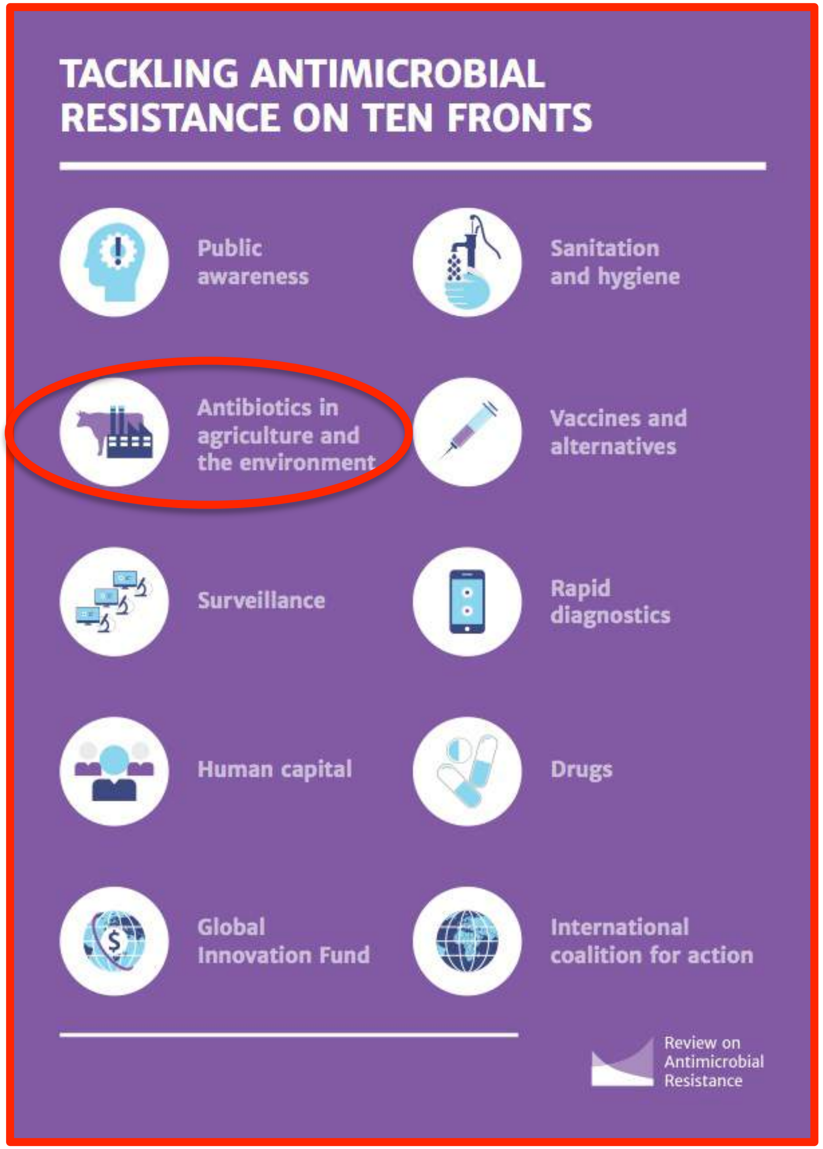

LOWERING DEMAND FOR ANTIMICROBIALS AND REDUCING UNNECESSARY USE
Public awareness
Sanitation and hygiene
Antibiotics in agriculture and the environment
Vaccines and alternatives
Rapid diagnostics
Human capital
Demand
Quantity
Review on Antimicrobial Resistance

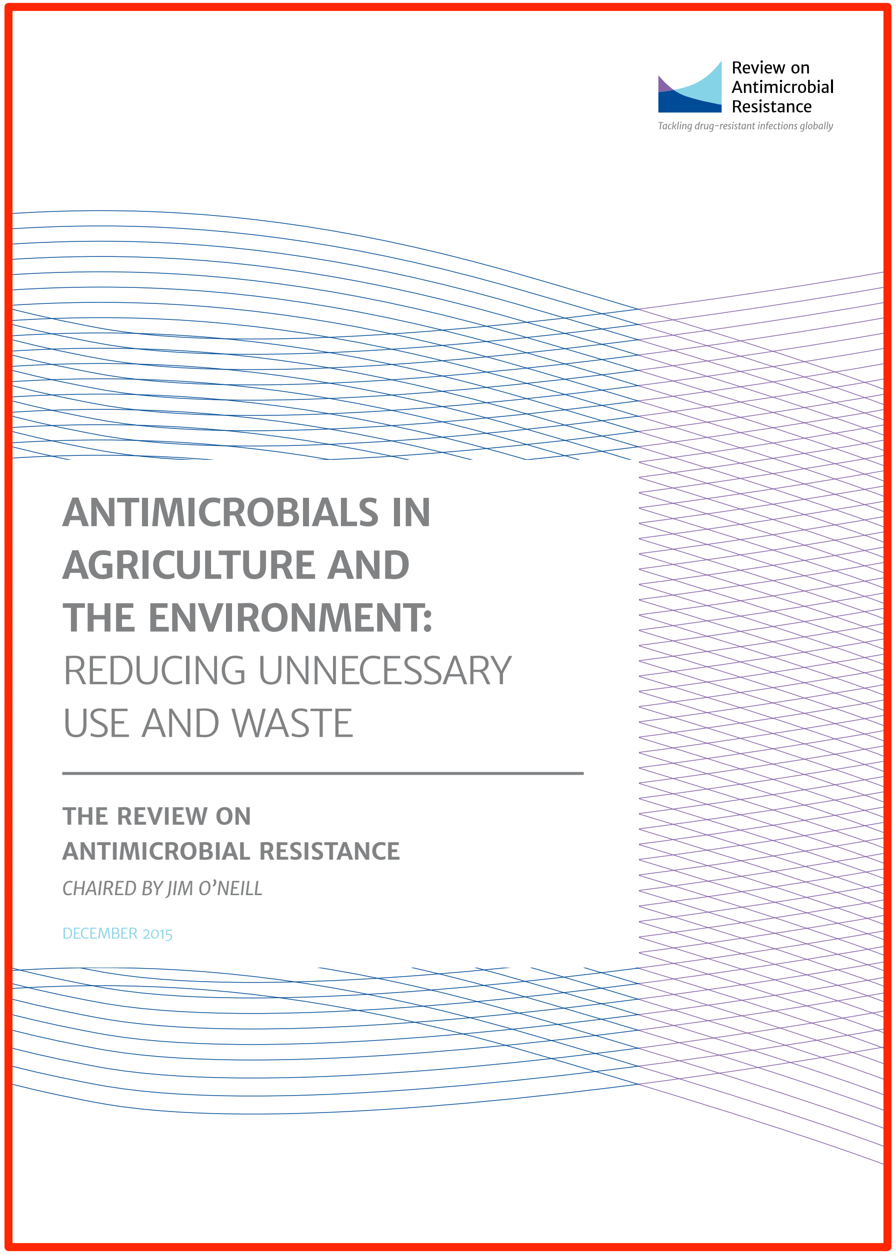

BETTER WATER AND SANITATION REDUCES ANTIBIOTIC CONSUMPTION
60%
potential decrease in the number of cases of water and sanitation-related diarrhoea being treated with antibiotics


RAPID DIAGNOSTICS WOULD REDUCE UNNECESSARY PRESCRIPTION
27m


INCREASING COVERAGE OF VACCINES CAN REDUCE ANTIBIOTIC USE
47%
reduction in antibiotic use


ALTERNATIVE PRODUCTS TO TACKLE INFECTIONS
Phage therapy
Lysins
Antibodies
Probiotics
Immune stimulation
Peptides



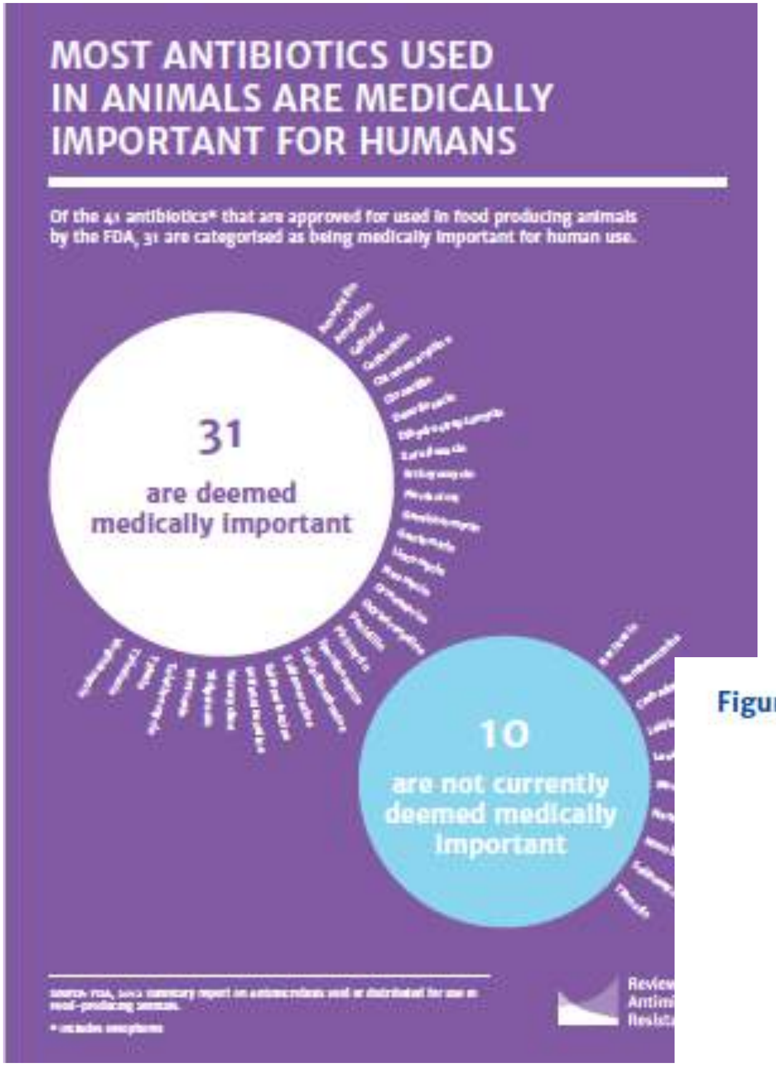

Review on Antimicrobial Resistance
Tackling drug-resistant infections globally

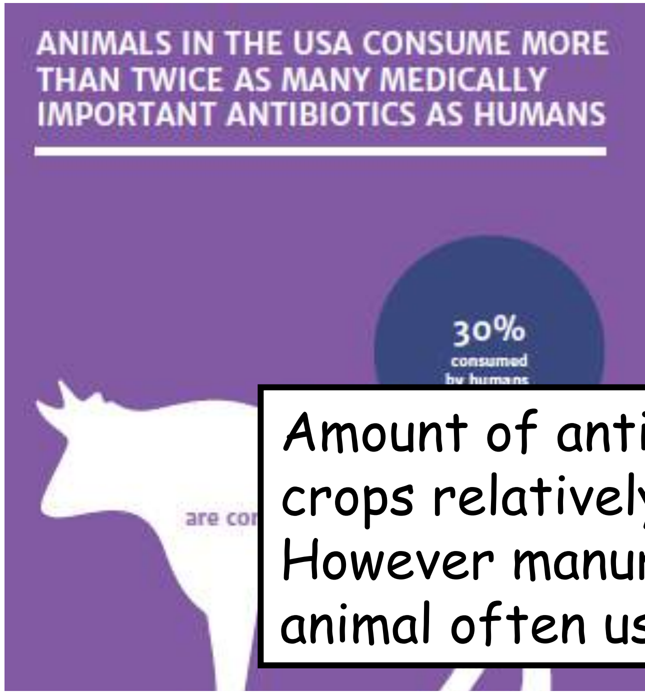
ANTIMICROBIALS IN AGRICULTURE AND THE ENVIRONMENT:
REDUCING UNNECESSARY USE AND WASTE

THE REVIEW ON ANTIMICROBIAL RESISTANCE
CHAIRED BY JIM O'NEILL

DECEMBER 2015

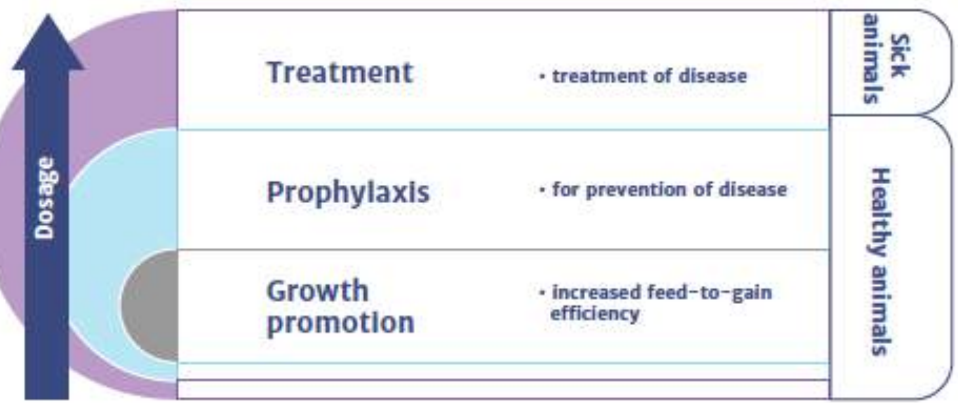
ANTIBIOTIC RESISTANCE: RISKS FROM LIVESTOCK





Amount of antibiotics used for crops relatively low
However manure from farm animal often used as fertilizer

Figure 1. Current uses of antibiotics in livestock

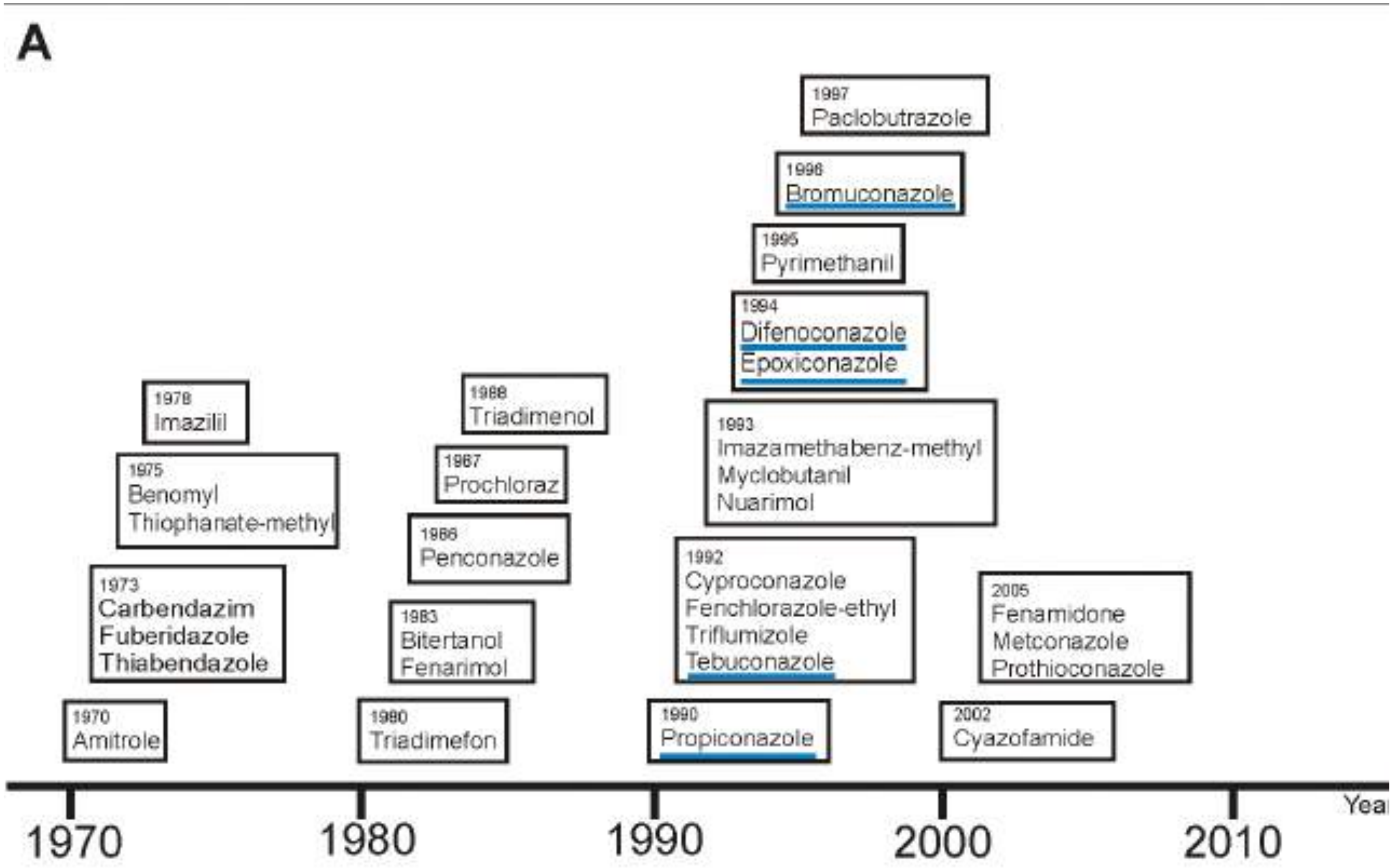


ANTIFUNGAL RESISTANCE: RISKS FROM CROPS

★ fungal diseases tend to pose much larger threats to crops

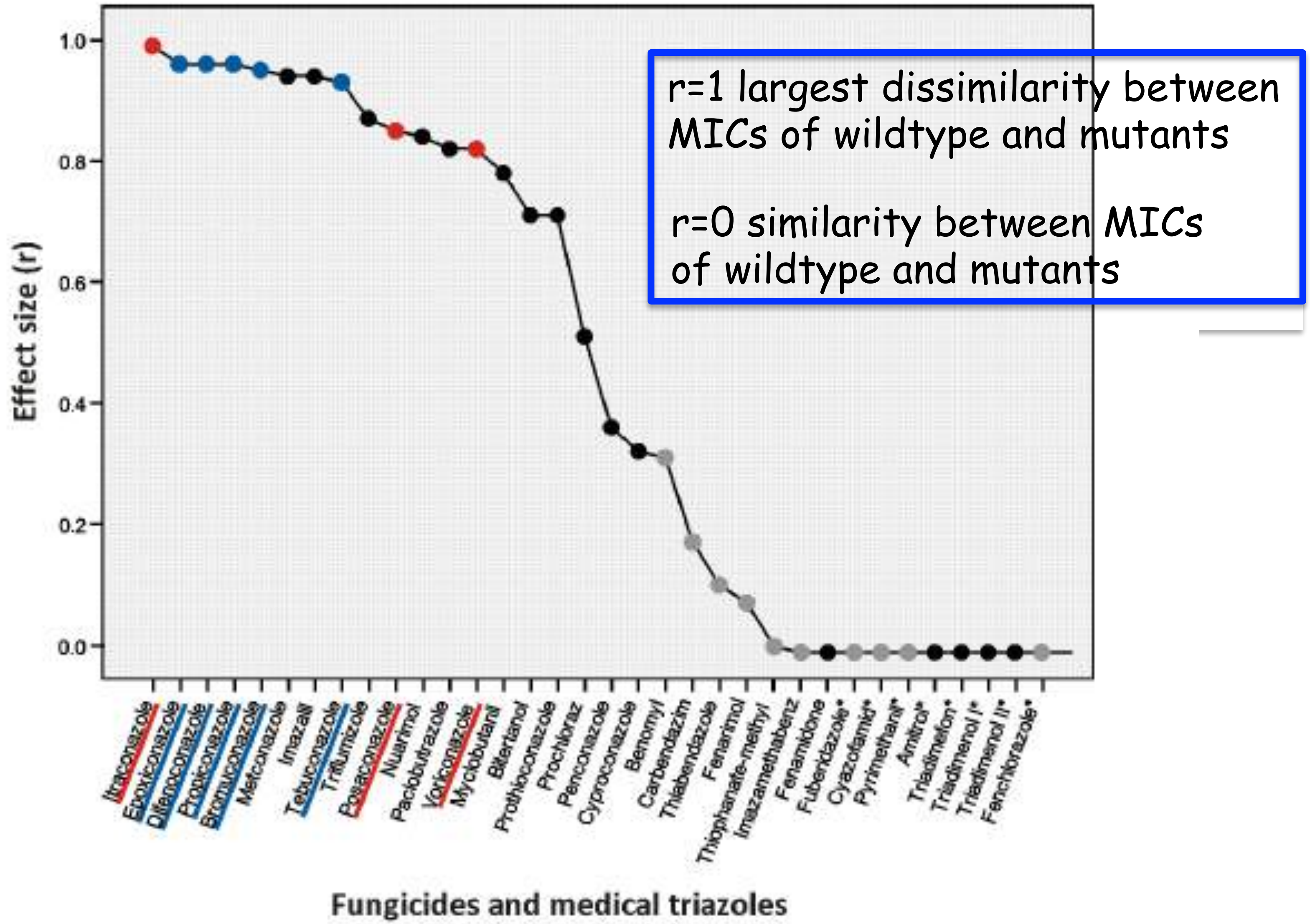
therefore

★ fungicides are used in significant quantities, in particular on cereals and grapes, but also in tulip production



Overview of compounds by year of authorization by the Dutch Board for the Authorization of Plant Protection Products and Biocides

Snelders E et al PlosOne 2012.



Correlation effect sizes (r) of compounds and medical triazoles comparing differences in the median MIC of wild types and TR_{34}/L98H isolates.

Snelders E et al PlosOne 2012.

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journal homepage: www.elsevier.com/locate/jhazmat

Fungicides induced triazole-resistance in *Aspergillus fumigatus* associated with mutations of TR46/Y121F/T289A and its appearance in agricultural fields

Jingbei Ren, Xiangxiang Jin, Qian Zhang, Yuan Zheng, Dunli Lin, Yunlong Yu*

Table 2
Susceptibility and the mutations of the induced resistant *A. fumigatus* to VRC, ITZ and POC after the gradually exposure to the triazole fungicides.

Strain No.	Strain No. after induction	Substrate	*Initial MIC* ($mg L^{-1}$)			*Final MIC* ($mg L^{-1}$)			Original Mutations[a]	Induced Mutations[b]
			VRC	*ITZ*	*POC*	*VRC*	*ITZ*	*POC*		
S3	S3R1	epoxiconazole	0.25	0.25	0.015	2	4	0.5		
	S3R2	tebuconazole	0.25	0.25	0.015	16	2	1		TR46/Y121F/T289A
S8	S8R3	propiconazole	0.25	0.125	0.125	16	1	1		TR46/Y121F/T289A
S12	S12R1	epoxiconazole	0.25	0.125	0.03125	16	1	0.25	N248K	A284T
	S12R3	propiconazole	0.25	0.125	0.03125	8	4	0.5	N248K	G448S
	S12R4	hexaconazole	0.25	0.125	0.03125	8	8	1	N248K	
S14	S14R1	epoxiconazole	0.25	0.125	0.0625	16	4	0.5		P222Q
	S14R3	propiconazole	0.25	0.125	0.0625	1	0.5	0.5		
	S14R4	hexaconazole	0.25	0.125	0.0625	2	1	1		
	S14R5	flutriafol	0.25	0.125	0.0625	16	0.5	1		
S15	S15R3	propiconazole	0.25	0.25	0.03125	8	8	1		
	S15R4	hexaconazole	0.25	0.25	0.03125	8	8	1		TR46/Y121F/T289A
S16	S16R1	epoxiconazole	0.25	0.25	0.0625	8	8	1		TR46/Y121F/T289A
S17	S17R1	epoxiconazole	0.25	0.25	0.0625	4	8	1		
	S17R6	metconazole	0.25	0.25	0.0625	4	2	0.5		TR46/Y121F/T289A
S18	S18R6	metconazole	0.25	0.25	0.0625	4	1	0.5		TR46/Y121F/T289A

[a] the original point mutation in *cyp51A* gene of the susceptible strains before the gradual exposure to the triazole fungicides. It was detected with the method mentioned in the section of material and methods.

[b] the mutations in *cyp51A* gene of the induced resistant *A. fumigatus* after the gradual exposure to the triazole fungicides.

Tavola 07 - Principi attivi contenuti nei prodotti fitosanitari per ettaro di superficie trattabile (in chilogrammi) . Dettaglio per ripartizione geografica - Anno 2015 [(a)] [(b)]

Ripartizioni geografiche	Fungicidi	Insetticidi e acaricidi	Erbicidi	Vari
Nord	5,91	1,02	1,60	1,06
Centro	3,03	0,26	0,60	1,04
Mezzogiorno	3,89	0,67	0,50	1,22
ITALIA	**4,46**	**0,72**	**0,91**	**1,13**

Principi attivi in Kg in differenti regioni italiane (2015)

	fungicidi/ ettaro	triazoli/ ettaro
Piemonte	5,39	0,07
Lombardia	1,80	0,08
Liguria	3,56	0,03
Trentino	30,23	0,25
Veneto	8,72	0,10
Friuli	6,83	0,08
Emilia	5,97	0,13
Toscana	4,12	0,03
Umbria	2,82	0,04
Marche	1,82	0,06
Lazio	2,83	0,04
Abruzzo	5,63	0,03
Molise	0,76	0,02
Campania	4,68	0,07
Puglia	3,97	0,06
Basilicata	2,17	0,03
Calabria	1,58	0,03
Sicilia	5,89	0,02
Sardegna	1,77	0,01

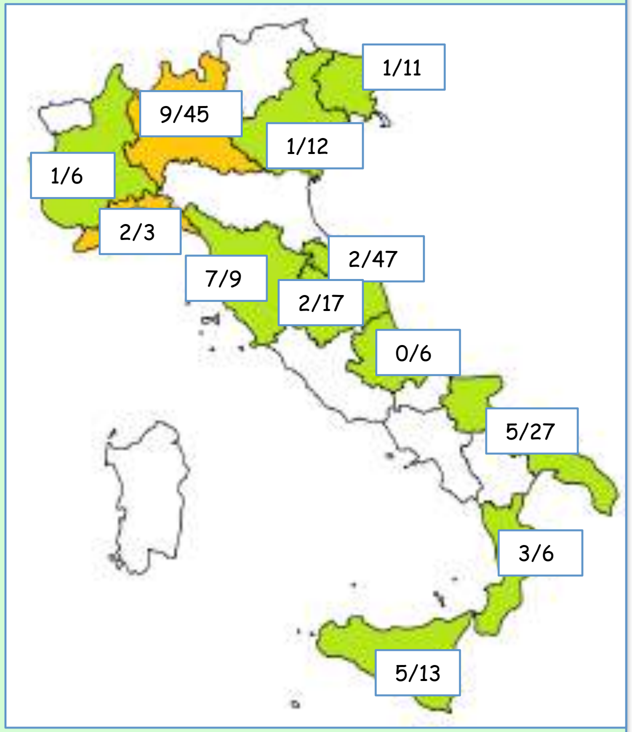
Aspergillus fumigatus: azole resistance in Italy

Environmental survey
(2011-12 and 2014-16)

Positive/sampled in each region

38/202 (18.8%)

37 TR_{34}/L98H
1 G54E

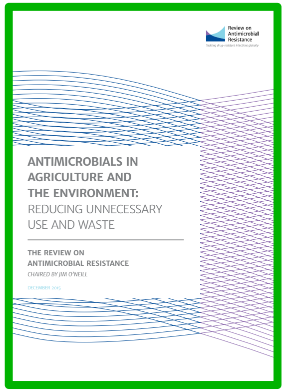


Ortaggi vari
Frutteti (meleti, uliveti, vigneti, aranceti)
Compost fiori
Grano

Regions in yellow: data from
Prigitano et al Eurosurveillance 2014

Regions in green: unpublished data

CONCLUSIONS


ANTIMICROBIALS IN
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- World food production relies heavily on fungicides and this make a full ban on their use very difficult. However
- New classes of clinical antifungals that are developed in future should be banned from use in food production
- Ban certain azoles from use in non-food crop production (tulip production)
- Greater surveillance of antifungal resistance
- More research into alternatives in fungicides
- Minimise resistance developing from their use

Grazie per l'attenzione