NOVEL DATA ON NEW AND OLD EPIDEMICS

CONFERENCE

Milan, 12 September 2023

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UNIVERSITÀ DEGLI STUDI DI MILANO

Sistema Socio Sanitario
Regione Lombardia
ASST Santi Paolo e Carlo

Conference
NOVEL DATA ON
NEW AND OLD EPIDEMICS
Milan, 12 September 2023
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Global strategies to contain MDR epidemics

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Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in Europe

- Estimated 671 689 (95% uncertainty interval [UI] 583 148–763 966) infections with antibiotic-resistant bacteria,
- of which 63·5% (426 277 of 671 689) were associated with health care.
- These infections accounted for an estimated 33 110 (28 480–38 430) attributable deaths and 874 541 (768 837–989 068) DALYs

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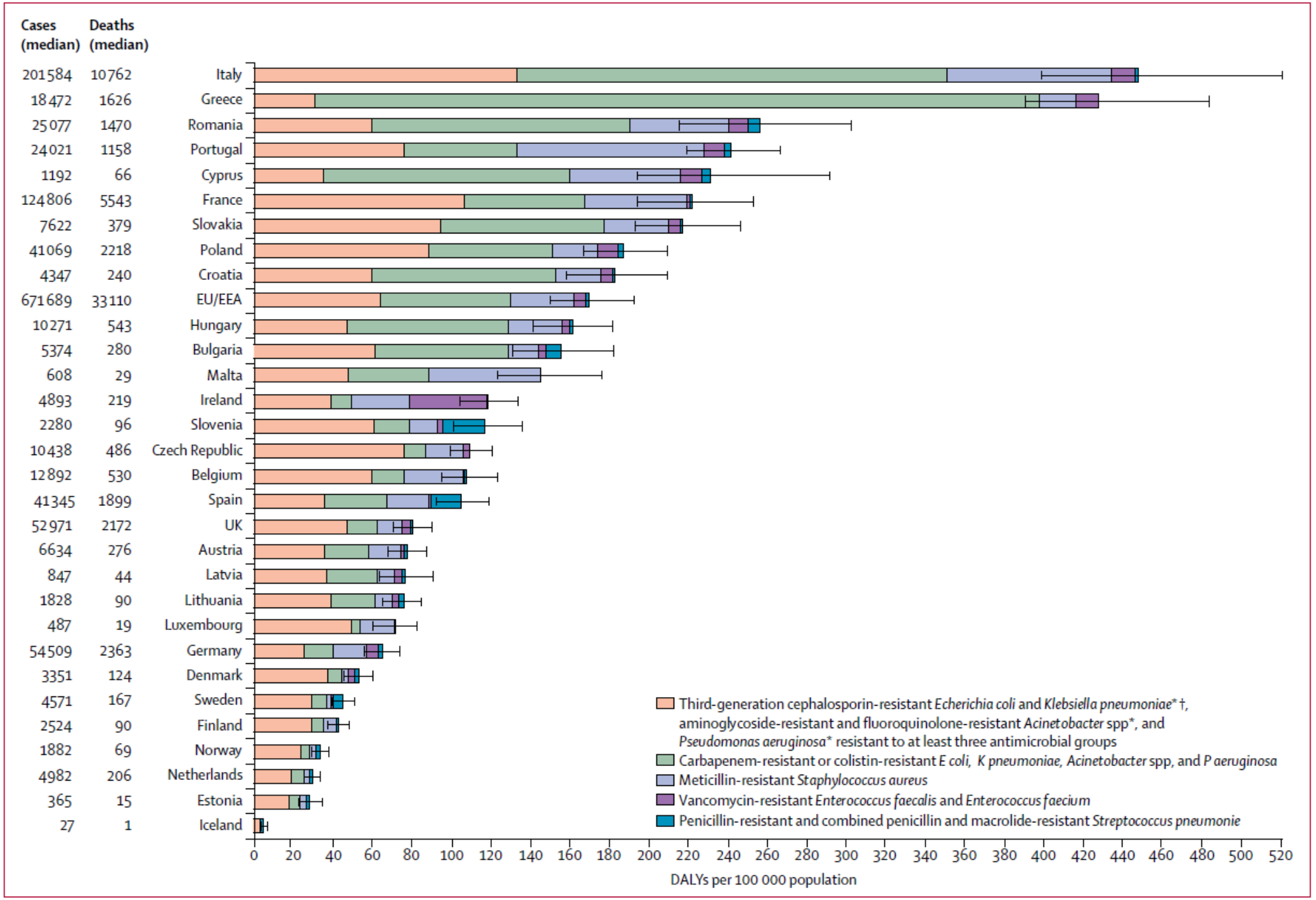
Cassini A Lancet Infect Dis 2019

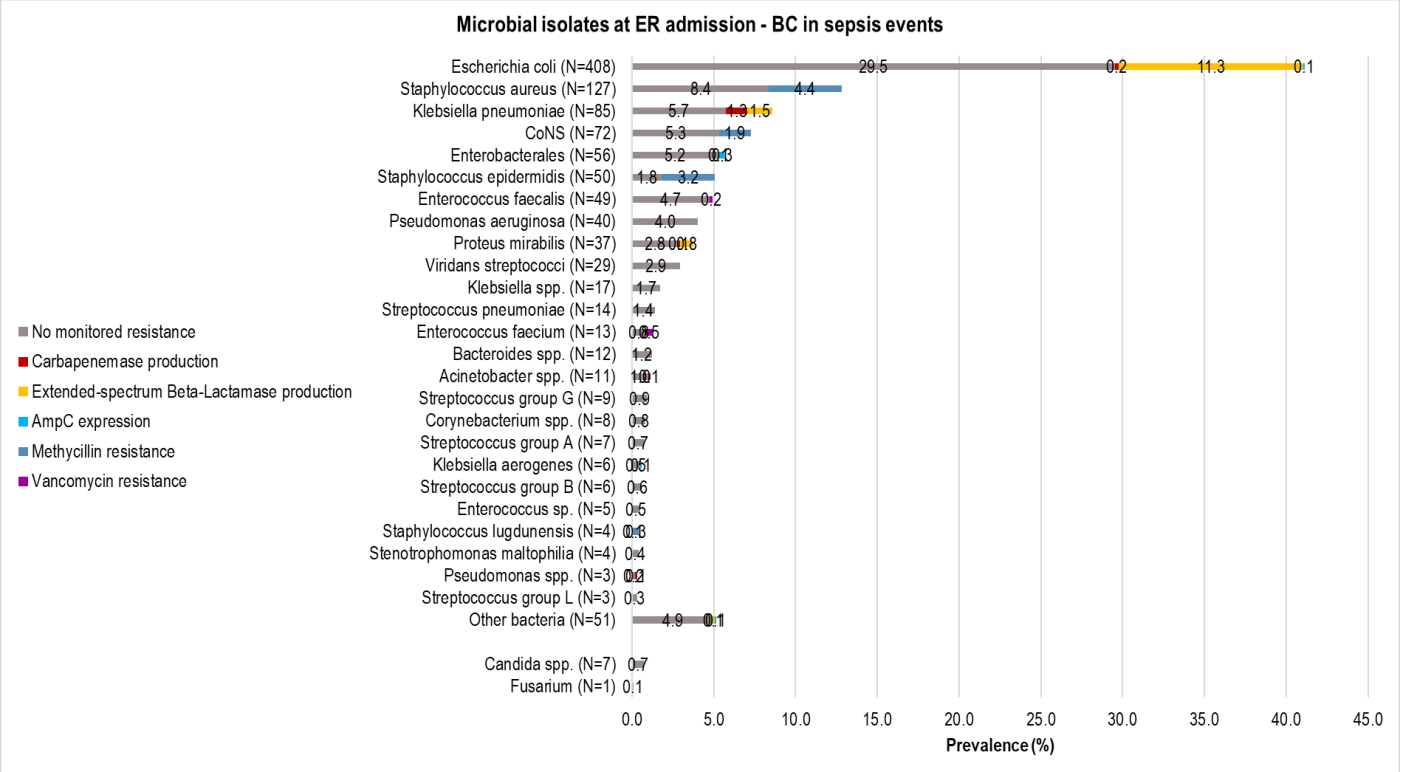


Cassini A Lancet Infect Dis 2019

Resistance profile of microorganisms involved in sepsis events in a Level-2 Emergency Department from 2015 to 2022

Cento V et al ECCMID 2023

- 2905 admission for sepsis
- BC performed 73% of cases
- ESBL-producing E.coli 12%
- MRSA 4.3%
- CRE 2%



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The Antibiotic Resistance Crisis

Ventola CL, Pharmacy and Therapeutics. 2015 Apr; 40(4): 277–283

CAUSES OF THE ANTIBIOTIC RESISTANCE CRISIS

1. Overuse
   - In some states, the number of prescribed courses of treatment with antibiotics per year
     exceed the population, amounting to more than one treatment per person per year
2. Inappropriate prescription
   - Studies have shown that treatment indication, choice of agent, or duration of antibiotic therapy is incorrect in 30% to 50% of cases

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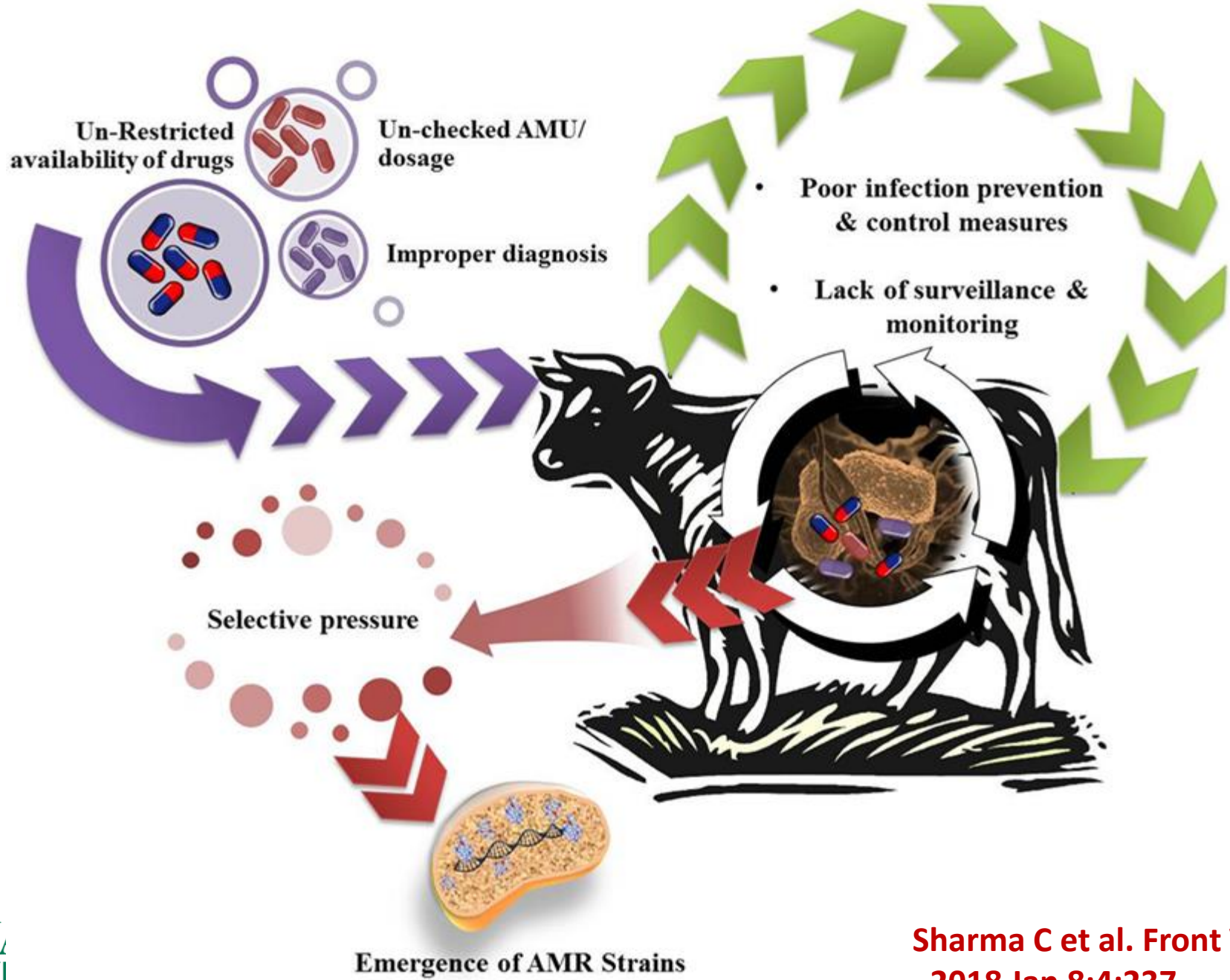

Sharma C et al. Front Vet Sci . 2018 Jan 8;4:237.

P1914

One Health approach to resistance of *Aspergillus fumigatus* to azoles in Hauts-de-France

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Results

1- Investigation of clinical *Aspergillus fumigatus* isolates

Table 2: Resistant isolates *Aspergillus fumigatus* from January 2019 to May 2022

Promoter/ *CYP51A* Sequencing	Number of resistant isolates (No of patients)	MIC ITC (EUCAST)	MIC VRC (EUCAST)	Type of sample	Underlying condition (s)
TR_{34}/L98H	15 (12)	≥8	2- >8	Expectoration (n=7), Sputum (n=6), BAL (n=2)	CF (n=5)/ CF-ABPA (n=2)/ Chronic pulmonary aspergillosis (n=2)/ Cirrhosis (n=1)/ IPA Haematology (n=1)/ IPA Intensive care (n=1)
TR_{46}/Y121F, T289A	1 (1)	>8	>8	BAL (n=1)	Haematological malignancy (n=1)
TR_{46}^{3}/Y121F, M172I, T289A, G448S	2 (1)	>8	>8	BAL (n=1), TP (n=1)	Intensive Care-IS (n=1)
WT/F219S	4 (1)	>8	4-8	Sputum (n=3), Expectoration (n=1)	CF (n=1)
WT/G170S	1 (1)	>8	2	BAL (n=1)	COVID (n=1)
WT/G54R	1 (1)	>8	0,5	BAL (n=1)	Chronic pulmonary aspergillosis (n=1)
WT/WT	1 (1)	1	2	Sputum (n=1)	CF-ABPA (n=1)

+ sequencing of two isolates in progress

ABPA : Allergic BronchoPulmonary Aspergillosis; BAL : Bronchoalveolar lavage; CF : Cystic fibrosis; IS : Immunosuppressed; ITC : Itraconazole; TP : Transparietal puncture; VRC : Voriconazole

- ✓ This preliminary results are focused on the period from January 2019 to May 2022.
- ✓ Investigation of azole-resistant phenotypes and genotypes are presented in **table 2**:
  - ✓ 25 azole-resistant *Aspergillus fumigatus* isolates from 17 patients
    - ✓ 18 isolates with environmental mutations
    - ✓ 12 patients with a home in the Somme department

2- Investigation of environmental use of fungicides

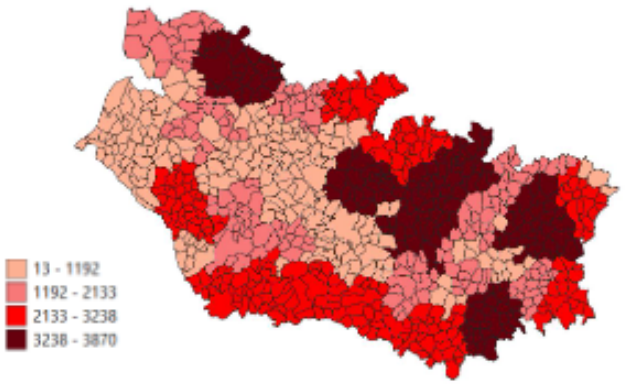

Figure 5: Purchase of azole fungicides in kg by postal code of the user for the Somme (BNVD 2020 data, software QGIS)

- ✓ It is interesting to note that only 3 of 12 the patients from the Somme department with environmental mutations live in areas where the use of azole fungicides is above 2133 kgs.

Conclusions/ Perspectives

18 of the 25 resistant isolates bear mutations in the *CYP51A* gene and its promotor, characteristic of environmental origin (TR_{34}/L98H, TR_{46}/Y121F,T289A, TR_{46}^{3}/Y121F,M172I,T289A,G448S). These data, taken together with high level purchase of fungicides in this area, confirm the need of an One Health approach to investigate azole resistance in *A. fumigatus*.
In order to better describe the areas of influence of resistance, soil samples will be taken in the department using a stratification based on cartography of fungicide use levels and patients' home localizations.

[1] BNVD 2020 « Banque nationale des données des ventes des distributeurs de produits phytosanitaires » (National database of sales data of distributors of plant protection products) https://ventes.produits-phytopharmaceutiques.eos/home.htmarsh
[2] https://www.ecologie.gouv.fr/sites/default/files/BNVD.pdf
[3] Fraaije et al. Curr Protein Microbiol. 2018
[4] Lavergne et al. Antimicrob Agents Chemother. 2015
[5] Alanio et al. J Antimicrob Chemother. 2011
[6] Morio et al. J Antimicrob Chemother. 2012
[7] Denning et al. Indoor Air. 2018

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33rd ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
Copenhagen, Denmark
15–18 April 2023

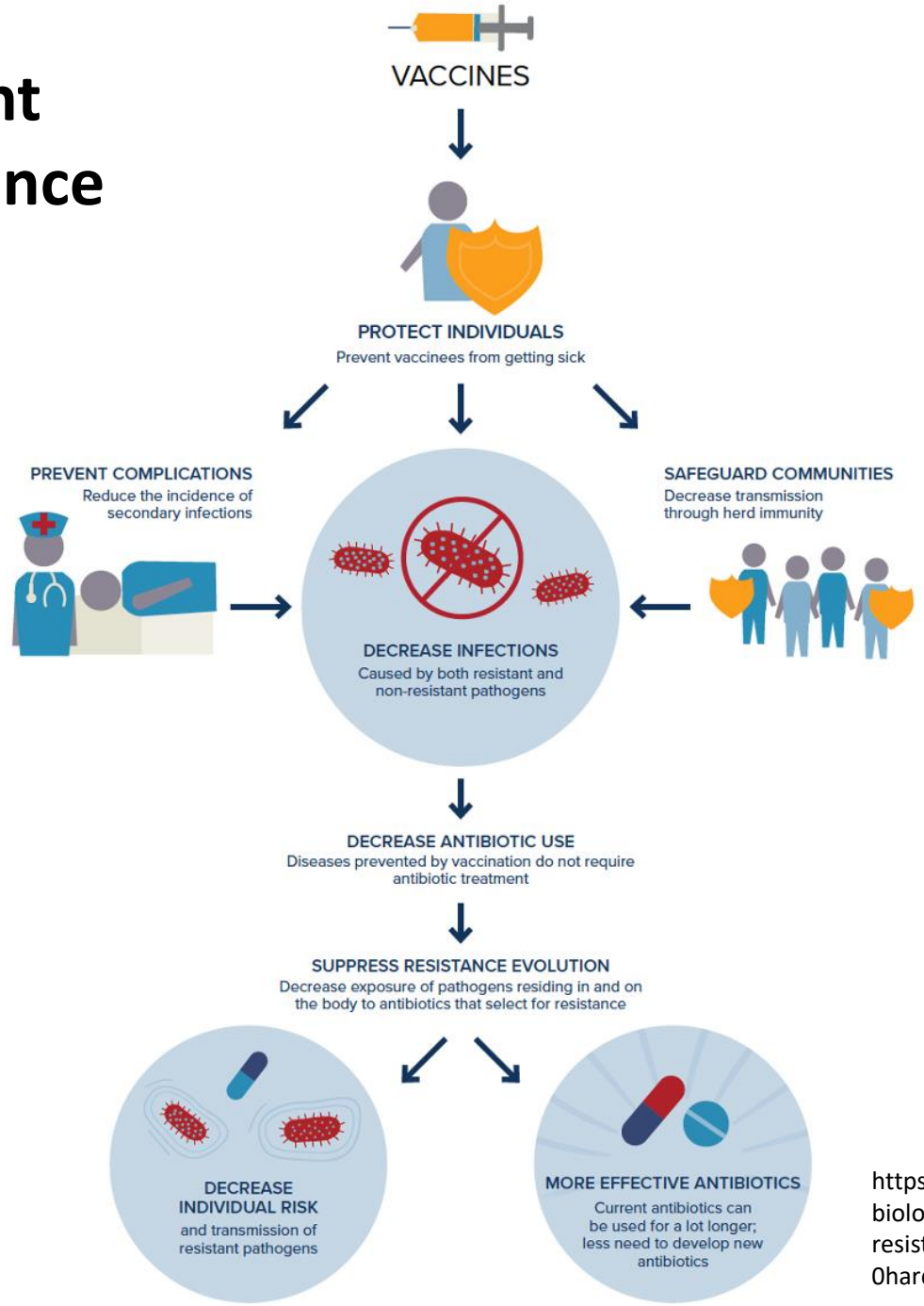
Strategies to contain antimicrobial resistance

1. Prevent infections

2. Improve use of antimicrobials

3. Stop the spread of resistance

Vaccines may prevent antimicrobial resistance



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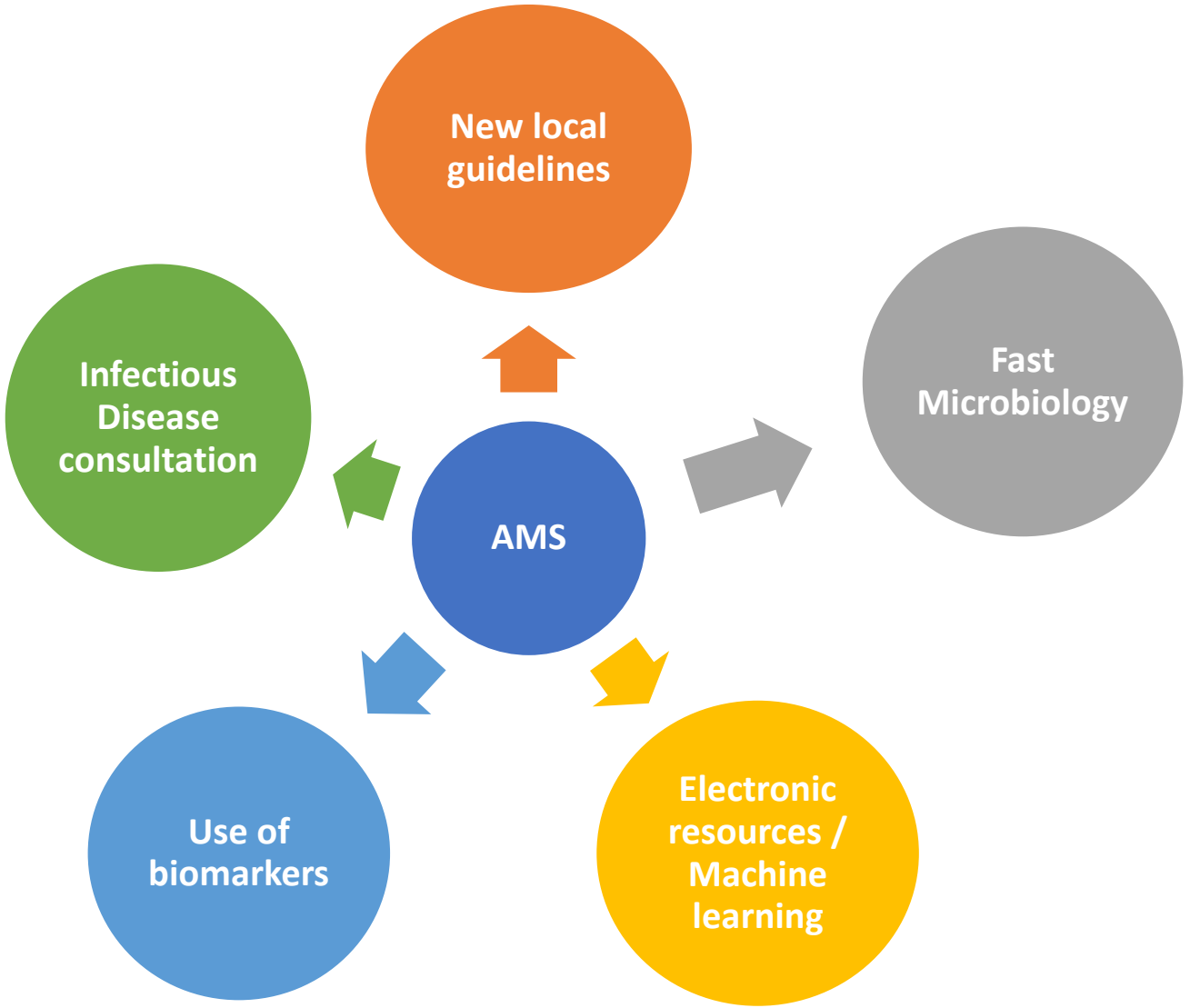
https://www.who.int/teams/immunization-vaccines-and-biologicals/product-and-delivery-research/anti-microbial-resistance#:~:text=Vaccines%20are%20an%20important%20tool,very%20hard%20to%20treat%20infections.

Improve use of antimicrobials



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Antimicrobial stewardship in the primary care setting: from dream to reality?

Avent LC et al BMC Fam Pract. 2020; 21: 134.

Core elements of AMS	AMS Interventions	Advantages	Disadvantages
Commitment	1. Commitment poster in support of AMS [15] displayed in the waiting room and openly endorsed by the practice and its clinicians	Well received by the public.Provides standardised guidance & support for clinicians at a practice level.Low-cost, effective intervention.	Requires collaboration of clinicians at a practice level.
Action for practices	1. Clinical decision support [16–19]	Reduces inappropriate antibiotic prescribing.	Need for an Electronic Health Record system to support a Clinical Decision support tool.Low uptake can be a barrier to effectiveness.
	2. Back-up (delayed or 'wait and see') prescribing [20–24]	Decreases antibiotic use.	Antibiotics can be utilized for conditions other than the original presentation.
	3. Point of care tests [25–30]	Decreases diagnostic uncertainty.Supports non-prescription decisions.Decreases inappropriate antibiotic use for viral infections.	Over-reliance or under-reliance on diagnostic tests.Difficulty of incorporating tests into current practice work flow.
Tracking and reporting	1. Personalized audit and feedback to prescribers of antibiotic-prescribing rates in comparison to peers [16, 31–34]2. Public reporting of antibiotic usage data [35]	Modifies prescribing behaviour.Reduces inappropriate prescribing.	Time consuming and increased resources are required for auditing process.Auditing process requires an Electronic Health Record system.Expertise required to validate and interpret data.
Education and expertise	Patient education. Shared decision making [36, 37]	Decreases antibiotic use.Improves patient satisfaction.	Time consuming for clinicians.
	Clinician educationb. Communication training [26, 33, 38, 39]c. Peer academic detailing [40]	Promotes acceptance of AMS strategies.T.Effective with sustained benefits over time.Active, in-person education more effective than didactic education.	Time consuming for clinicians.Lack of uptake by clinicians.

Prescription Strategies in Acute Uncomplicated Respiratory Infections: A Randomized Clinical Trial

De la Poza Abad JAMA Intern Med . 2016 Jan;176(1):21-9.

Table 3. Duration of Patient Symptoms After First Visit[a]

Characteristic	Duration of Symptoms per Prescription Strategy, d, Mean (SD)				Overall *P* Value
	Immediate	Collection	Patient-Led	No Prescription	
Any until disappearance	11.7 (8.4)	12.3 (7.3)	13.1 (8.5)	14.4 (8.1)[b]	.02
Moderate (3 or 4)[c]	4.7 (4.0)	5.2 (4.3)[b,d]	6.0 (5.5)[b]	6.5 (5.2)[b]	<.001
Severe (5 or 6)[c]	3.6 (3.3)	4.0 (4.2)[b]	5.1 (6.3)[b]	4.7 (3.6)[b]	.002
Common symptoms					
Fever	3.7 (4.2)	3.8 (3.2)[d]	3.8 (3.7)[d]	5.4 (6.3)[b]	.004
Discomfort or general pain	6.7 (5.7)	8.7 (7.0)[b]	7.9 (7.1)[b,d]	10.2 (7.1)[b]	.002
Cough	10.0 (6.6)	9.6 (6.7)	11.1 (8.0)	12.3 (8.1)[b]	.03
Difficulty sleeping	6.0 (6.2)	6.5 (5.2)	8.3 (7.1)	7.6 (6.2)	.11
Changes in everyday life	6.4 (6.4)	6.6 (5.5)	6.9 (6.3)	8.4 (6.6)	.14

C-Reactive Protein Testing to Guide Antibiotic Prescribing for COPD Exacerbations

Butler NEJM 2019

- ✓ DESIGN: Multicenter, open-label, randomized, controlled trial
- ✓ POPULATION: Patients with a diagnosis of COPD in their primary care
- ✓ INTERVENTION:
  1. usual care + CRP point-of-care testing (CRP-guided group)
  2. or usual care alone (usual-care group).
- ✓ ENDPOINT:
  1. The primary outcomes were patient-reported use of antibiotics for acute exacerbations of COPD within 4 weeks after randomization (to show superiority)
  2. COPD-related health status at 2 weeks after randomization,

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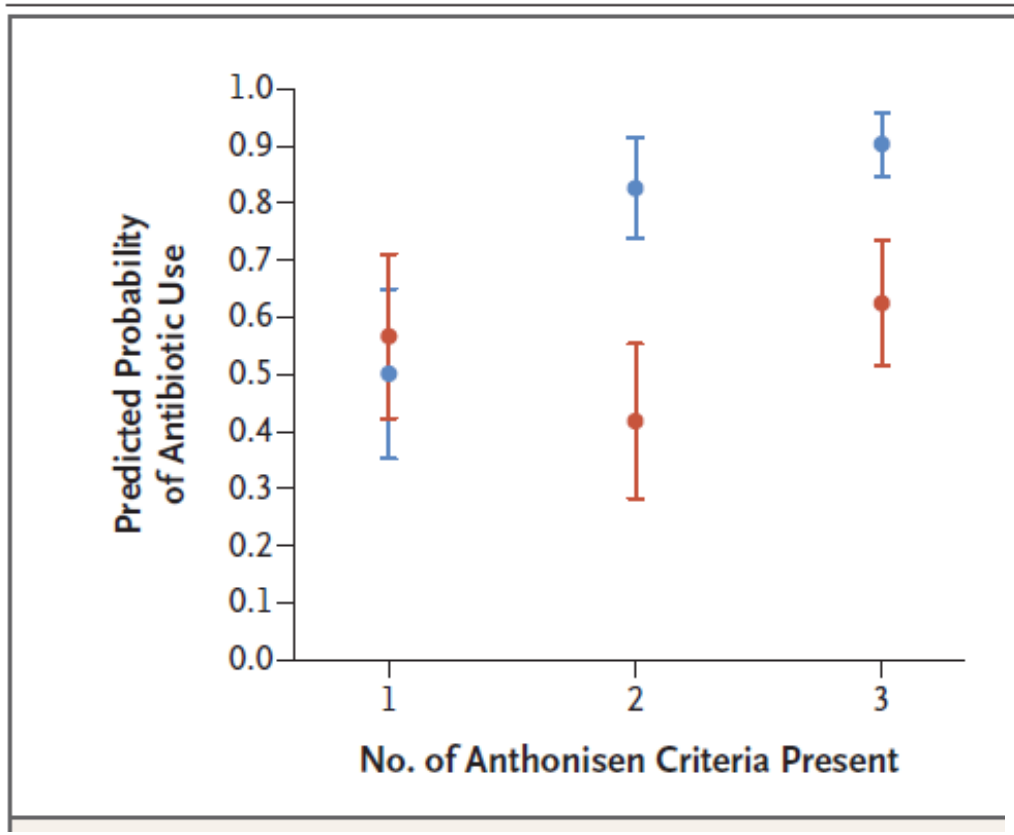
C-Reactive Protein Testing to Guide Antibiotic Prescribing for COPD Exacerbations

Butler NEJM 2019

Use of antibiotics

(57.0% vs. 77.4%; adjusted odds ratio, 0.31; 95% confidence interval [CI], 0.20 to 0.47).



Assessment

Severity of exacerbation based on symptoms

Definition Elements	Severity

• Worsening dyspnea
• Increased sputum purulence
• Increase in sputum volume
	• Type I (Severe) - all 3 elements
	• Type II (Moderate) - 2 elements
	• Type III (Mild) - 1 element plus:
	  • URI in past 5 days
	  • Fever without apparent cause
	  • Increased wheezing or cough
	  • Increase (+20%) of respiratory rate or heart rate

Modified from Anthonisen et al. Ann Int Med 106:196, 1987

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Implementation of point-of-care testing of C-reactive protein concentrations to improve antibiotic targeting in respiratory illness in Vietnamese primary care: a pragmatic cluster-randomised controlled trial

LNga Thi Thuy Do, PhDancet Infect Dis 2023; 23: 1085–94

	Control group	Intervention group	Adjusted relative risk (95% CI)	Adjusted risk difference (95% CI)
Population				
Intention to treat	20 860/21 235 (98·2%)	17 345/18 621 (93·1%)	0·83 (0·66 to 0·93)	−7 (−8 to −6)
Per protocol*	20 860/21 235 (98·2%)	1859/2606 (71·3%)	0·64 (0·60 to 0·70)	−30 (−36 to −30)
Age group, years				
1–15	5679/5835 (97·3%)	4585/4901 (93·6%)	0·86 (0·62 to 0·97)	−14 (−36 to −3)
16–65	15 181/15 400 (98·6%)	12 760/13 720 (93·0%)	0·82 (0·66 to 0·93)	−17 (−34 to −7)
C-reactive protein concentration, mg/L*				
<10	..	650/1274 (51·0%)	0·45 (0·41 to 0·49)	−54 (−58 to −50)
10 to ≤40	..	1000/1121 (89·2%)	0·87 (0·83 to 0·89)	−13 (−16 to −10)
>40	..	209/211 (99·1%)	1·00 (0·95 to 1·02)	0 (−5 to 1)
Gender				

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Impact of rapid species identification on management of bloodstream infections

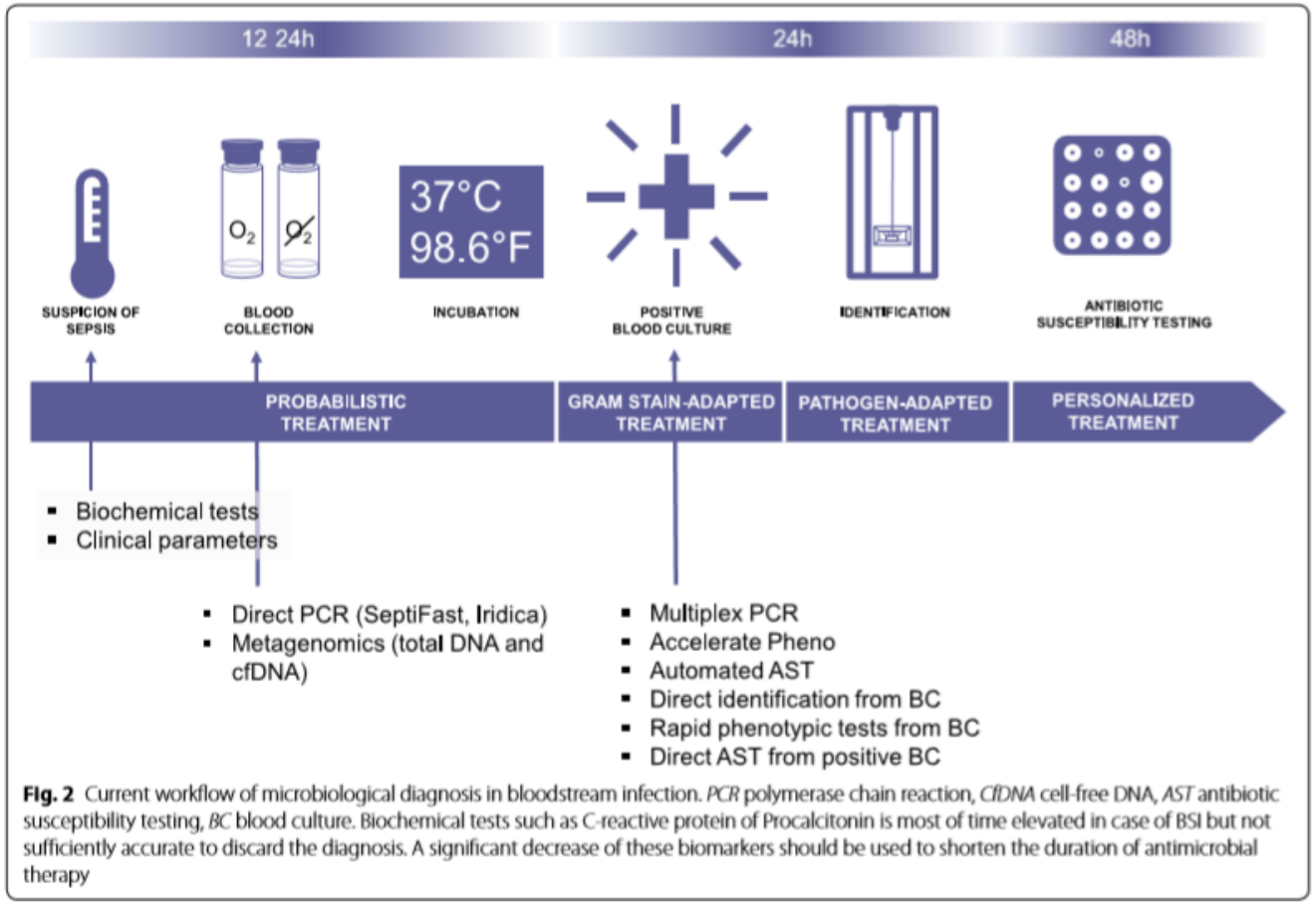

Fig. 2 Current workflow of microbiological diagnosis in bloodstream infection. *PCR* polymerase chain reaction, *CfDNA* cell-free DNA, *AST* antibiotic susceptibility testing, *BC* blood culture. Biochemical tests such as C-reactive protein of Procalcitonin is most of time elevated in case of BSI but not sufficiently accurate to discard the diagnosis. A significant decrease of these biomarkers should be used to shorten the duration of antimicrobial therapy

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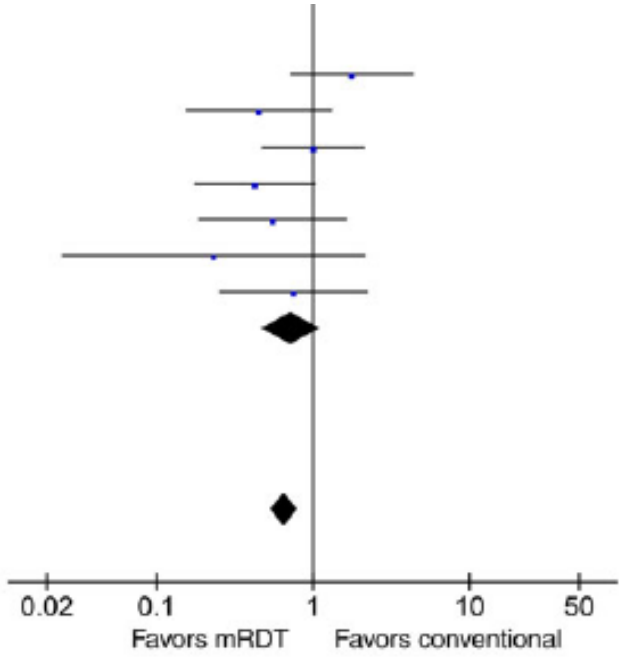
Timsit et al., Intensive Care Med. (2020) 46:266-284. https://doi.org/10.1007/s00134-020-05950-6

The Effect of Molecular Rapid Diagnostic Testing on Clinical Outcomes in Bloodstream Infections: A Systematic Review and Meta-analysis

Timbrook CID 2017:64

Effect of RDT in Bloodstream infections without antimicrobial stewardship program (ASP)

1.1.2 mRDT without ASP						
Beuving et al [18] (2015)	14	114	8	109	4.1	1.77 (.71–4.40)
Felsenstein et al [22] (2016)	5	189	11	194	3.0	0.45 (.15–1.33)
Frye et al [26] (2012)	14	110	17	134	5.7	1.00 (.47–2.14)
Ly et al [31] (2008)	8	101	17	101	4.2	0.43 (.17–1.04)
Maslonka et al [34] (2014)	6	55	10	55	2.9	0.55 (.19–1.64)
Neuberger et al [37] (2008)	1	42	4	42	0.7	0.23 (.02–2.17)
Wang et al [46] (2013)	8	48	8	38	2.9	0.75 (.25–2.23)
Subtotal		659		673	23.5	**0.72 (.46–1.12)**
Total events	56		75			
Heterogeneity: $\tau^2 = 0.08$ $\chi^2 = 7.74$ ($df = 6$; $P = .26$); $I^2 = 23\%$						
Test for overall effect: $z = 1.46$ ($P = .15$)						
Total (95% CI)		2404		2731	100.0	**0.66 (.54– .80)**
Total events	233		406			
Heterogeneity: $\tau^2 = 0.02$ $\chi^2 = 27.22$ ($df = 25$; $P = .34$); $I^2 = 8\%$						
Test for overall effect: $z = 4.27$ ($P < .001$)						
Test for subgoup differences: $\chi^2 = 0.25$ ($df = 1$; $P = .62$); $I^2 = 0\%$						



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The Effect of Molecular Rapid Diagnostic Testing on Clinical Outcomes in Bloodstream Infections: A Systematic Review and Meta-analysis

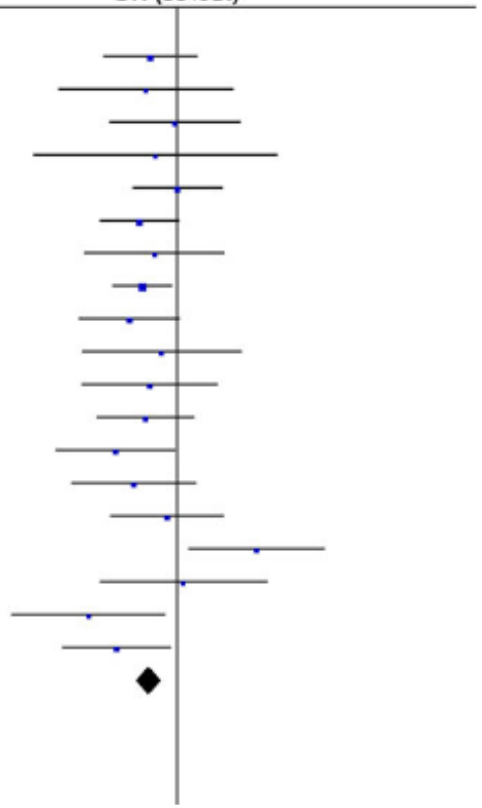
Timbrook CID 2017:64

Combining RDT and Antimicrobial stewardship program (ASP)

	mRDT		Conventional Testing			
Study or Subgroup	Events	Total	Events	Total	Weight, %	OR (95%CI)
1.1.1 mRDT with ASP						
Bauer et al [17] (2010)	15	82	19	74	5.6	0.65 (.30–1.39)
Bias et al [19] (2015)	3	37	7	55	1.8	0.61 (.15–2.51)
Box et al [20] (2015)	6	64	10	103	3.0	0.96 (.33–2.79)
Forrest et al [24] (2006)	2	119	2	84	0.9	0.70 (.10–5.08)
Forrest et al [23] (2006)	19	72	20	76	6.0	1.00 (.48–2.09)
Forrest et al [25] (2008)	17	95	37	129	7.4	0.54 (.28–1.04)
Heil et al [27] (2012)	5	21	19	61	2.7	0.69 (.22–2.16)
Huang et al [29] (2013)	31	245	52	256	11.8	0.57 (.35–.92)
Lockwood et al [30] (2016)	11	241	14	149	4.9	0.46 (.20–.1.04)
Macvane et al [32] (2015)	5	63	5	50	2.1	0.78 (.21–.2.84)
Macvane et al [33] (2016)	6	23	16	45	2.8	0.64 (.21–.1.95)
Nagel et al [36] (2014)	11	117	19	129	5.3	0.60 (.27–.1.32)
Pardo et al [39] (2016)	5	84	37	252	3.6	0.37 (.14–.97)
Perez et al [15] (2013)	6	107	12	112	3.3	0.50 (.18–1.37)
Revolinksi et al [40] (2015)	8	95	13	133	4.0	0.85 (.34–2.14)
Sango et al [42] (2013)	11	28	7	46	2.8	3.61 (1.19–10.89)
Sothoron et al [43] (2015)	5	67	4	59	1.9	1.11 (.28–4.34)
Suzuki et al [44] (2015)	3	88	19	147	2.3	0.24 (.07– .83)
Walker et al [45] (2016)	8	97	19	98	4.3	0.37 (.16– .90)
Subtotal		**1745**		**2058**	**76.5**	**0.64 (.51– .79)**
Total events	177		331			

Heterogeneity: $\tau^2 = 0.01$ $\chi^2 = 19.00$ ($df = 18$; $P = .39$); $I^2 = 5\%$

Test for overall effect: $z = 4.14$ ($P < .001$)



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Artificial Intelligence for Antimicrobial Resistance Prediction: Challenges and Opportunities towards Practical Implementation

Ali et al Antibiotics 2023, 12, 523. https:// doi.org/10.3390/antibiotics12030523

Table 1. Different ML/DL models and their merits and demerits in AMR problem applications.

Technique	Algorithm	Advantages		Disadvantages	
Neural Networks (simple Neural networks, RNN, CNN etc.) [38,60–66]	These models mimic the human brain and learn by optimizing weights until the final objective is achieved. The better the data, the better is performance Can perform on multi-dimensional data	✓ ✓ ✓ ✓	Can solve complex problems Feature interaction Can evaluate features Capable of multivariate features	× ×	Increased model complexity with increase in layers and nodes The model is not traceable
Decision Tree [28,72,73]	Predict based on target. Leaf nodes equal class label, nodes in the model equals to attributes	✓ ✓ ✓	Can evaluate features Model is traceable Feature interaction	×	Model might suffer with increasing feature complexity/multivariate
Logistic Regression [74]	Logistic curve that associates to each input features	✓	Feature evaluation	× ×	Non-traceable Interaction of features is not possible

Machine Learning to Assess the Risk of MultidrugResistant Gram-Negative Bacilli Infections in Febrile Neutropenic Hematological Patients

Garcia-vidal C. et al Infect Dis Ther (2021) 10:971–983

- Retrospective study of almost 7 million pieces of structured data from all consecutive episodes of FN in hematological patients in a tertiary hospital in Barcelona (January 2008-December 2017).
- Conventional multivariate analysis and ML algorithms (random forest, gradient boosting machine, XGBoost, and GLM) were done.

Table 2 Metrics of ML models to predict the need for MDR-GNB coverage in patients with FN in the test set

Models	AUC	F1 score	Sensitivity	Specificity	Negative predictive value	Positive predictive value
GBM	0.7872	0.9705	0.4583	0.9988	0.9438	0.9778
XGBoost	0.7945	0.9670	0.4895	0.9886	0.9464	0.8246
Random forest	0.7896	0.9711	0.4583	1.00	0.9439	1.0
GLM	0.7827	0.9716	0.4687	1.00	0.9449	1.0

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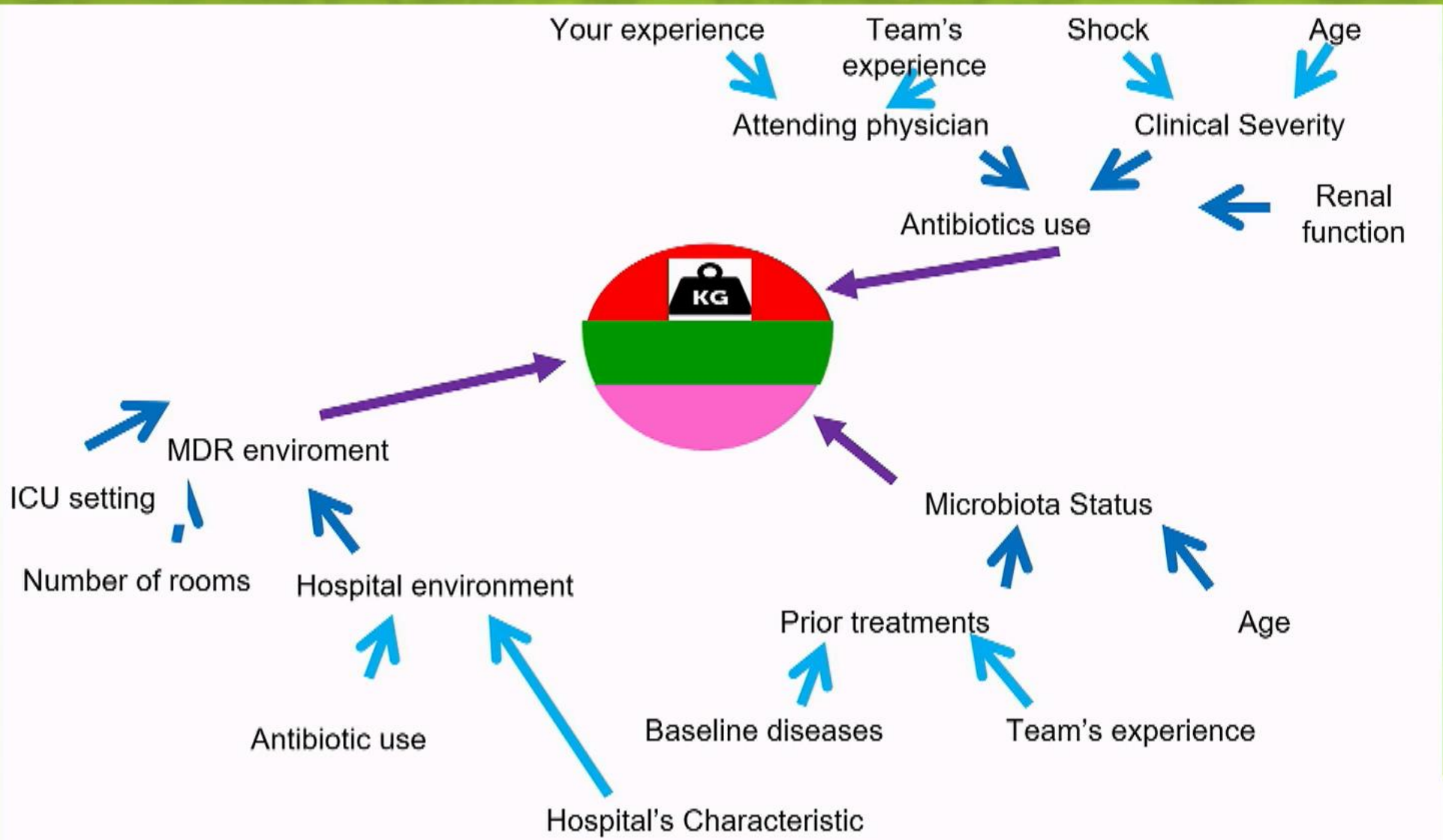
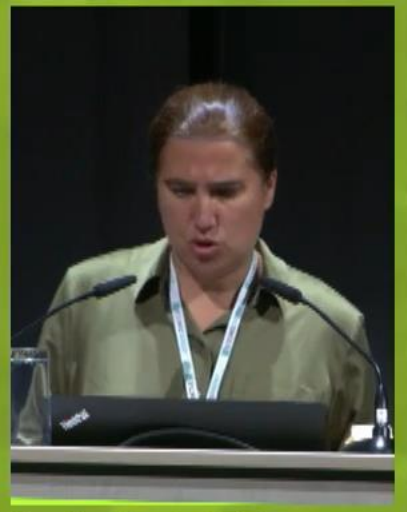
Statistic tools





Carolina Garcia Vidal
Spain

THANK YOU

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