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Giangiacomo Nicolini
Belluno

È vero che la vaccinazione antinfluenzale contribuisce alla riduzione dell'antimicrobico resistenza?

PEDIATRIA BELLUNO

SITIP SOCIETÀ ITALIANA DI INFETTIVOLOGIA PEDIATRICA

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vaccines

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Review

Specific and Nonspecific Effects of Influenza Vaccines

Nicola Principi [1] and Susanna Esposito [2,*]

* 1 bilione di casi stagionali di influenza
* La maggior parte sintomi lievi in assenza di febbre
* 20 – 40% : sintomi tradizionali (febbre, fairingodinia, tosse, cefalea, dolori muscolari e articolari, malessere)
* 3 – 5 milioni: patologia severa che conduce a ricovero
* 290.000 – 650.000 morti
* Soggetti a rischio: bambini < 5 anni, anziani, donne in gravidanza, patologie croniche invalidanti, immunodeficit
* Impatto sociale, economico e sanitario elevatissimo
* l'utilizzo del vaccino, specie nei bambini piccoli, ha ridotto enormemente costi diretti ed indiretti

Vaccines **2024**, *12*, 384. https://doi.org/10.3390/vaccines12040384

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* Molte nazioni hanno introdotto il vaccino antinfluenzale nella schedula vaccinale ufficiale, ed i dati epidemiologici confermano efficacia, tollerabilità e netta riduzione dei casi annuali di influenza e complicanze
* Tali studi evidenziano anche come la vaccinazione antinfluenzale possa controllare l'antibiotico resistenza (AMR)

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REVIEW

The impact of human vaccines on bacterial antimicrobial resistance. A review

Kathrin U. Jansen[1] · William C. Gruber[1] · Raphael Simon[1] · James Wassil[2,3] · Annaliesa S. Anderson[1]

- »Nella battaglia tra l'uomo e i batteri, vinceranno i batteri» (E. Concia)
- The introduction of antibiotics in the 1940 and 1950s placed evolutionary pressure on microorganisms to adapt developing AMR
- this trend has accelerated over time, with recognition of the shortening of the intervals from introduction of a new antibiotic to first documented cases of resistance
- AMR spread has been further exacerbated due to globalization that served as a vehicle for rapid transmission of emerging antibiotic-resistant microbial strains and associated resistance plasmids across continents (i.e. the spread of fluoroquinolone-resistant *Clostridioides,* methicillin- and fluoroquinolone-resistant *Staphylococcus aureus* strains)
- The excessive and irresponsible use of antimicrobials in healthcare, agriculture, and the food industry has fueled the dramatic rise of AMR globally

Environmental Chemistry Letters (2021) 19:4031–4062
https://doi.org/10.1007/s10311-021-01274-z

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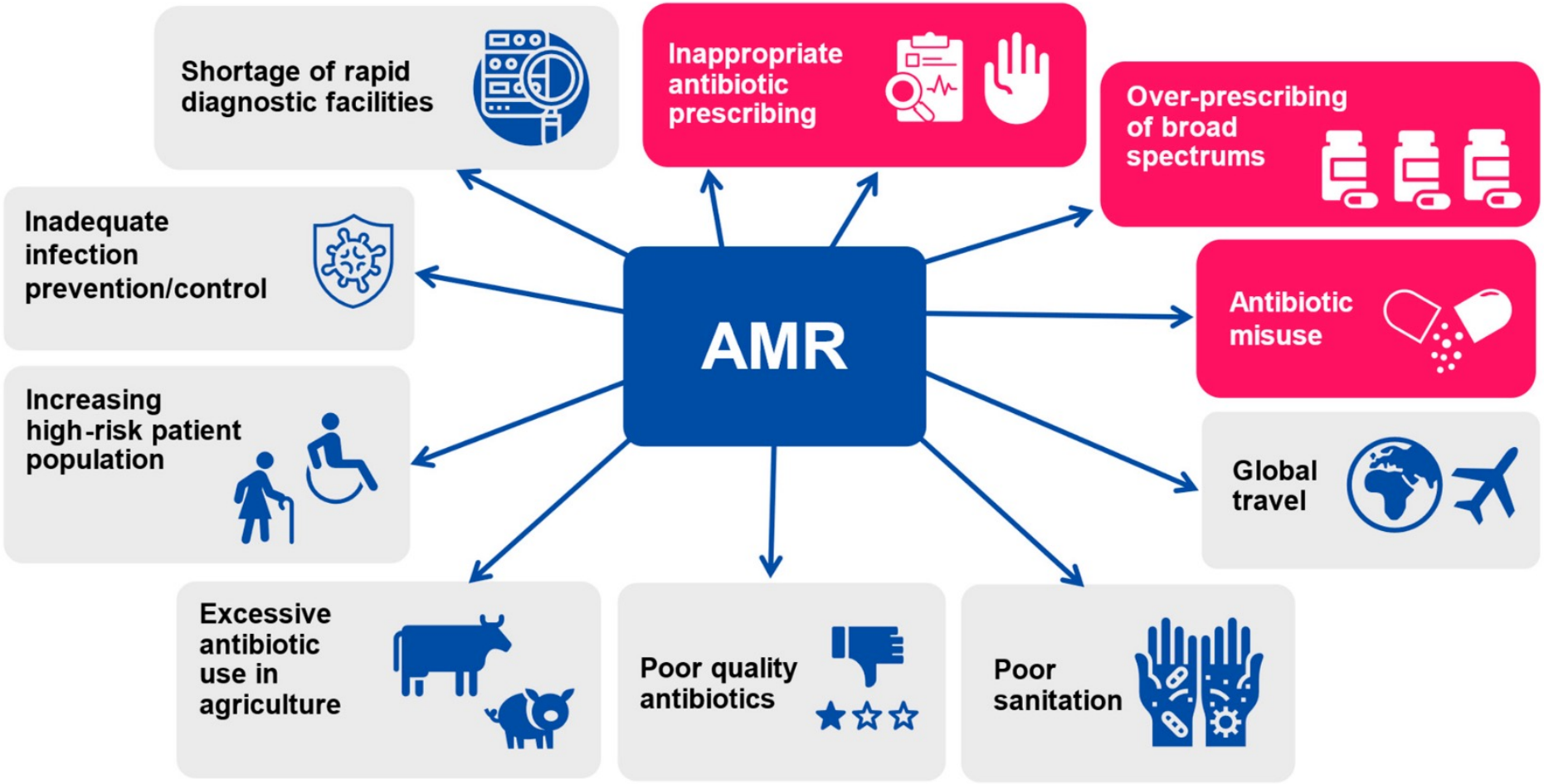

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* at least 700,000 people die of infections with AMR pathogens every year, with up to 50,000 deaths occurring in the U.S. and Europe alone
* it is estimated that annually, 10 million people worldwide will succumb to an AMR infection by 2050, exceeding the number of deaths from cancer
* In 2013, CDC published a list of antibiotic - resistant pathogens in the U.S. which were stratified into urgent, serious, and concerning threat tiers based on the threat they pose to human health and urgency of the need for new and effective modalities for their treatment and prevention

New: update 2024

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CDC		WHO	
Urgent threats	Carbapenem-resistant *Acinetobacter*	Critical priority	*Acinetobacter baumannii*, carbapenem resistant
	Candida auris		*Pseudomonas aeruginosa*, carbapenem resistant
	Clostridioides difficile		
	Carbapenem-resistant *Enterobacteriaceae*		*Enterobacteriaceae**, carbapenem resistant, 3rd-generation cephalosporin resistant
	Drug-resistant *Neisseria gonorrhoeae*		
Serious threats	Drug-resistant *Campylobacter*	High priority	*Enterococcus faecium*, vancomycin resistant
	Drug-resistant *Candida*		*Staphylococcus aureus*, methicillin resistant, vancomycin intermediate and resistant
	Extended spectrum β-lactamase producing *Enterobacteriaceae*		*Helicobacter pylori*, clarithromycin resistant
	Vancomycin-resistant *Enterococcus*		*Campylobacter*, fluoroquinolone resistant
	Multidrug-resistant *Pseudomonas aeruginosa*		*Salmonella* spp., fluoroquinolone resistant
	Drug-resistant non-typhoidal *Salmonella*		*Neisseria gonorrhoeae*, 3rd-generation cephalosporin resistant, fluoroquinolone resistant
	Drug-resistant *Salmonella* serotype Typhi		
	Drug-resistant *Shigella*		
	Methicillin-resistant *Staphylococcus aureus*		
	Drug-resistant *Streptococcus pneumoniae*		
	Drug-resistant *Mycobacterium tuberculosis*		
Concerning threats	Erythromycin-resistant Group A *Streptococcus*	Medium priority	*Streptococcus pneumoniae*, penicillin nonsusceptible
	Clindamycin-resistant Group B *Streptococcus*		*Haemophilus influenzae*, ampicillin resistant
			Shigella spp., fluoroquinolone resistant
Watch list	Azole-resistant *Aspergillus fumigatus*		
	Drug-resistant *Mycoplasma genitalium*		
	Drug-resistant *Bordetella pertussis*		

https://www.who.int/publications/i/item/9789240093461

*Enterobacteriaceae include: *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter* spp., *Serratia* spp., *Proteus* spp., *Providencia* spp, and *Morganella* spp

CDC, Centers for Disease Control and Prevention; WHO, World Health Organization

Adapted from (Centers for Disease Control and Prevention 2019; World Health Organization 2017a)

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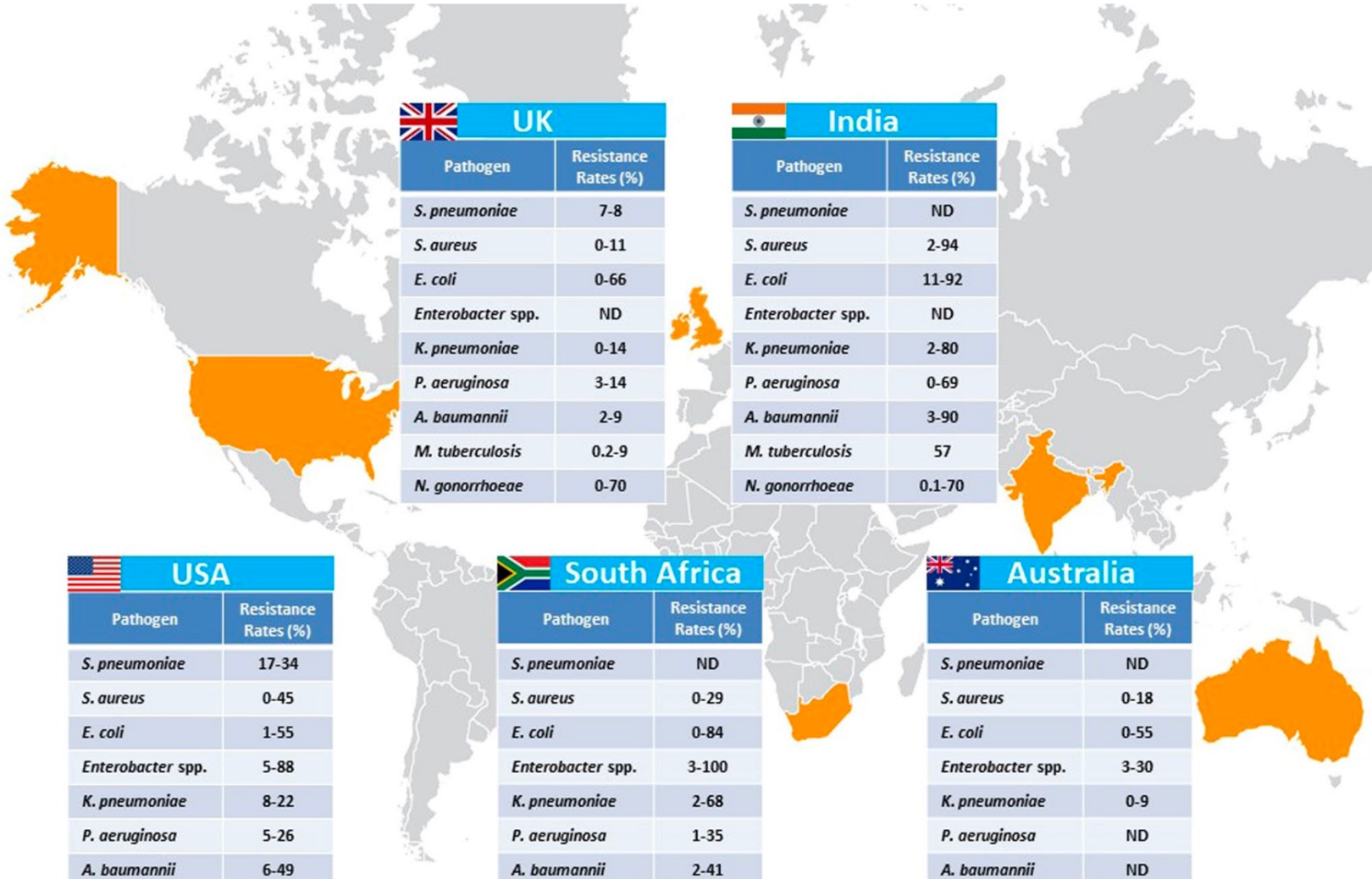

UK

Pathogen	Resistance Rates (%)
S. pneumoniae	7-8
S. aureus	0-11
E. coli	0-66
Enterobacter spp.	ND
K. pneumoniae	0-14
P. aeruginosa	3-14
A. baumannii	2-9
M. tuberculosis	0.2-9
N. gonorrhoeae	0-70

India

Pathogen	Resistance Rates (%)
S. pneumoniae	ND
S. aureus	2-94
E. coli	11-92
Enterobacter spp.	ND
K. pneumoniae	2-80
P. aeruginosa	0-69
A. baumannii	3-90
M. tuberculosis	57
N. gonorrhoeae	0.1-70

USA

Pathogen	Resistance Rates (%)
S. pneumoniae	17-34
S. aureus	0-45
E. coli	1-55
Enterobacter spp.	5-88
K. pneumoniae	8-22
P. aeruginosa	5-26
A. baumannii	6-49
M. tuberculosis	0-3
N. gonorrhoeae	0.1-30

South Africa

Pathogen	Resistance Rates (%)
S. pneumoniae	ND
S. aureus	0-29
E. coli	0-84
Enterobacter spp.	3-100
K. pneumoniae	2-68
P. aeruginosa	1-35
A. baumannii	2-41
M. tuberculosis	100
N. gonorrhoeae	0.1-70

Australia

Pathogen	Resistance Rates (%)
S. pneumoniae	ND
S. aureus	0-18
E. coli	0-55
Enterobacter spp.	3-30
K. pneumoniae	0-9
P. aeruginosa	ND
A. baumannii	ND
M. tuberculosis	0-2.9
N. gonorrhoeae	0.1-70

* To address the AMR crisis, a number of international organizations, including the WHO, the United Nations General Assembly, the World Bank, the G7, the G20, and the EU, as well as the U.S. and United Kingdom (UK) governments have been urgently developing strategic action plans to address the rising AMR issues.
* Among the proposed measures against AMR, these organizations emphasize the importance of prudent use of existing antimicrobials, and development of new effective antimicrobial medicines and vaccines for human and animals

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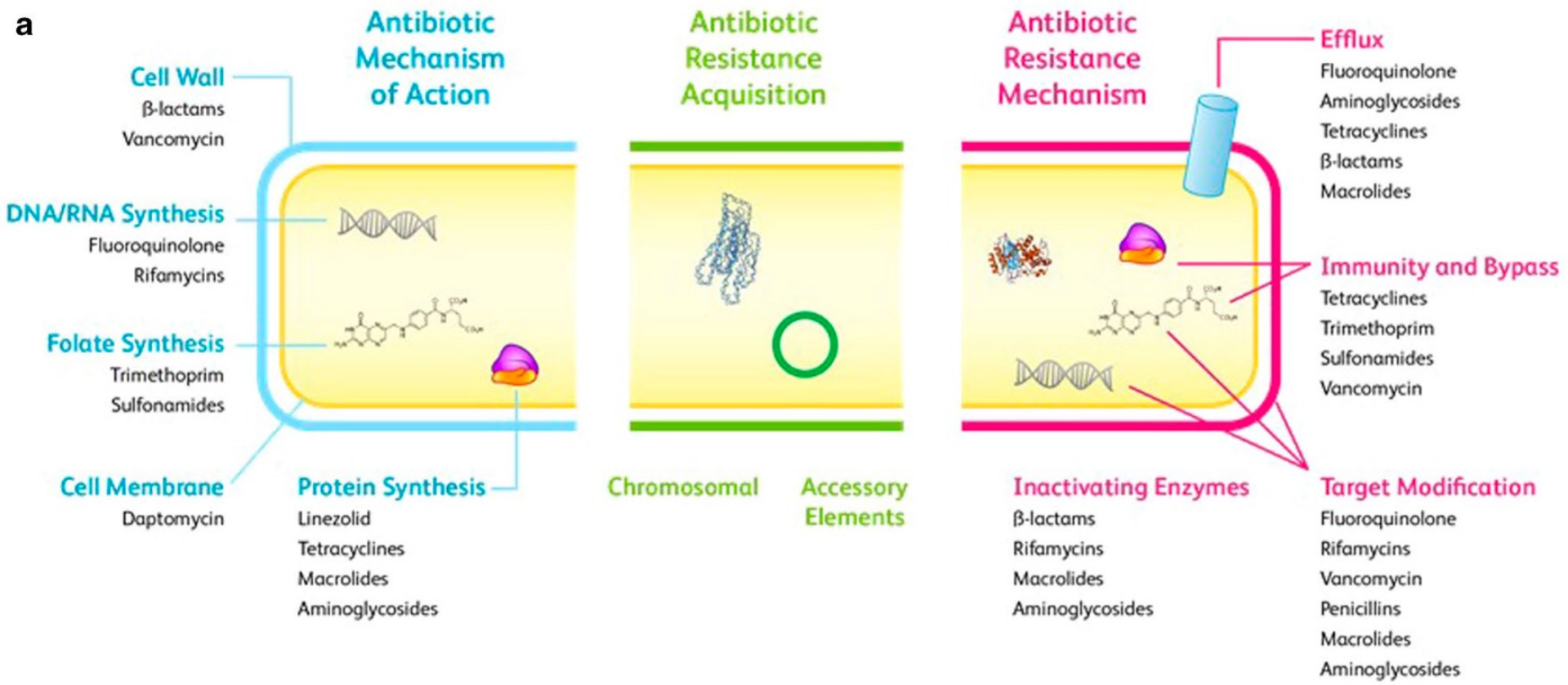

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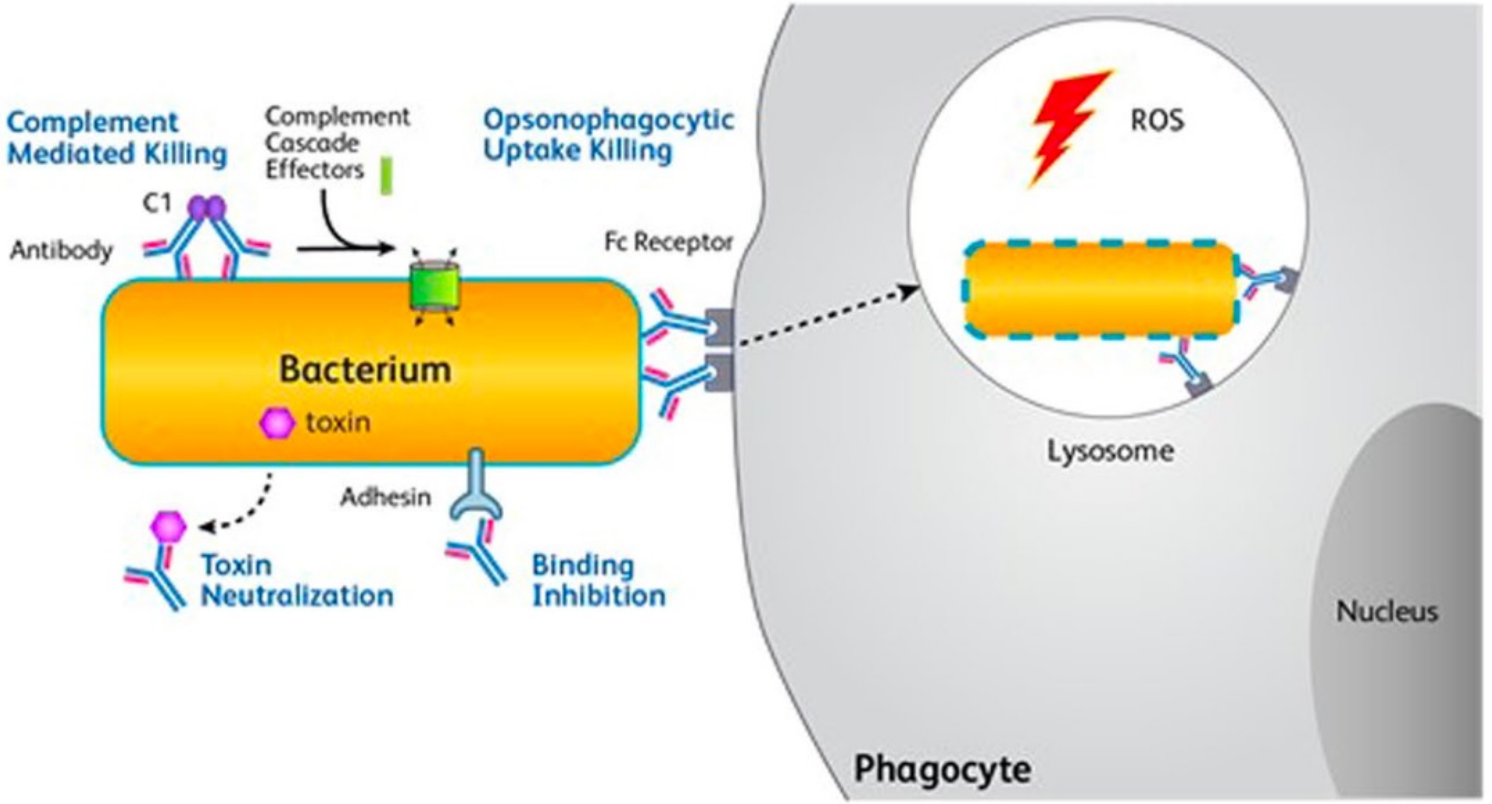

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Meccanismi tramite cui i vaccini prevengono AMR

1. impediscono l'instaurarsi dell'infezione sostenuta dal ceppo batterico di cui il germe MDR fa parte impedendo quindi l'infezione del germe MDR stesso
2. riducono il numero totale di infezioni di un ceppo batterico (agendo su batteri sensibili e non) e quindi la necessità di trattamenti antibiotici
3. possono ridurre la colonizzazione e non solo le infezioni da patogeni MDR
4. riducono lo sviluppo di infezioni da batteri MDR anche in soggetti non vaccinati mediante meccanismi di immunità di gregge (*herd immunity*)
5. anche i vaccini che prevengono infezioni virali come l'influenza sono in grado di combattere l'AMR dal momento che riducono il numero di malattie ad eziologia virale evitando quindi terapie antibiotiche inappropriate o necessarie a trattare sovra-infezioni batteriche
6. i vaccini in ambito veterinario sono potenzialmente in grado di ridurre l'utilizzo degli antibiotici negli allevamenti animali

1.O'Neill J. Vaccines and alternative approaches: reducing our dependence on antimicrobials. The review on antimicrobial resistence. London: HM Government and the Wellcome Trust; 2016.
2.Lipsitch M and Siber GR. How Can Vaccines Contribute to Solving the Antimicrobial Resistance Problem? MBio. 2016 Jun 7;7(3).
3.Mishra RP, Oviedo-Orta E, Prachi P, et al. Vaccines and antibiotic resistance. Curr Opin Microbiol. 2012 Oct;15(5):596-602.
4.World Health Organization (WHO). Why is vaccination important for addressing antibiotic resistance?
5.Klugman KP. Vaccination: a novel approach to reduce antibiotic resistance. Clin Infect Dis. 2004 Sep 1;39(5):649-51.

* Vaccination can affect AMR both directly and indirectly
  * Bacterial vaccines directly reduce antibiotic use through prevention of bacterial infections, and thus selection for AMR strains (DIRECT)
  * Viral vaccines also diminish antibiotic use through avoidance of unwarranted antibiotic prescriptions as well as through prevention of secondary bacterial infections (INDIRECT)
  * Additionally, bacterial vaccines decrease circulation of resistant strains in vaccinated populations in regions with adequate vaccine coverage (herd immunity)

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Efficacia diretta dei vaccini


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	Hib	Pneumococco	S. typhi
Incidenza pre vaccino	49 – 601 per 100.000	1,6 x 10^6 morti/anno	21.7 x 10^6 infetti 216.000 morti
Resistenza abx	⬆	⬆ e 63.000 casi di m. invasiva nel 2016	⬆
Incidenza post vaccino	0.19 per 100.000	⬇ 90% dopo PCV7	11.9 x 10^6 infetti 129.000 morti
Resistenza abx	⬇ 50%	⬇ 87%	⬇

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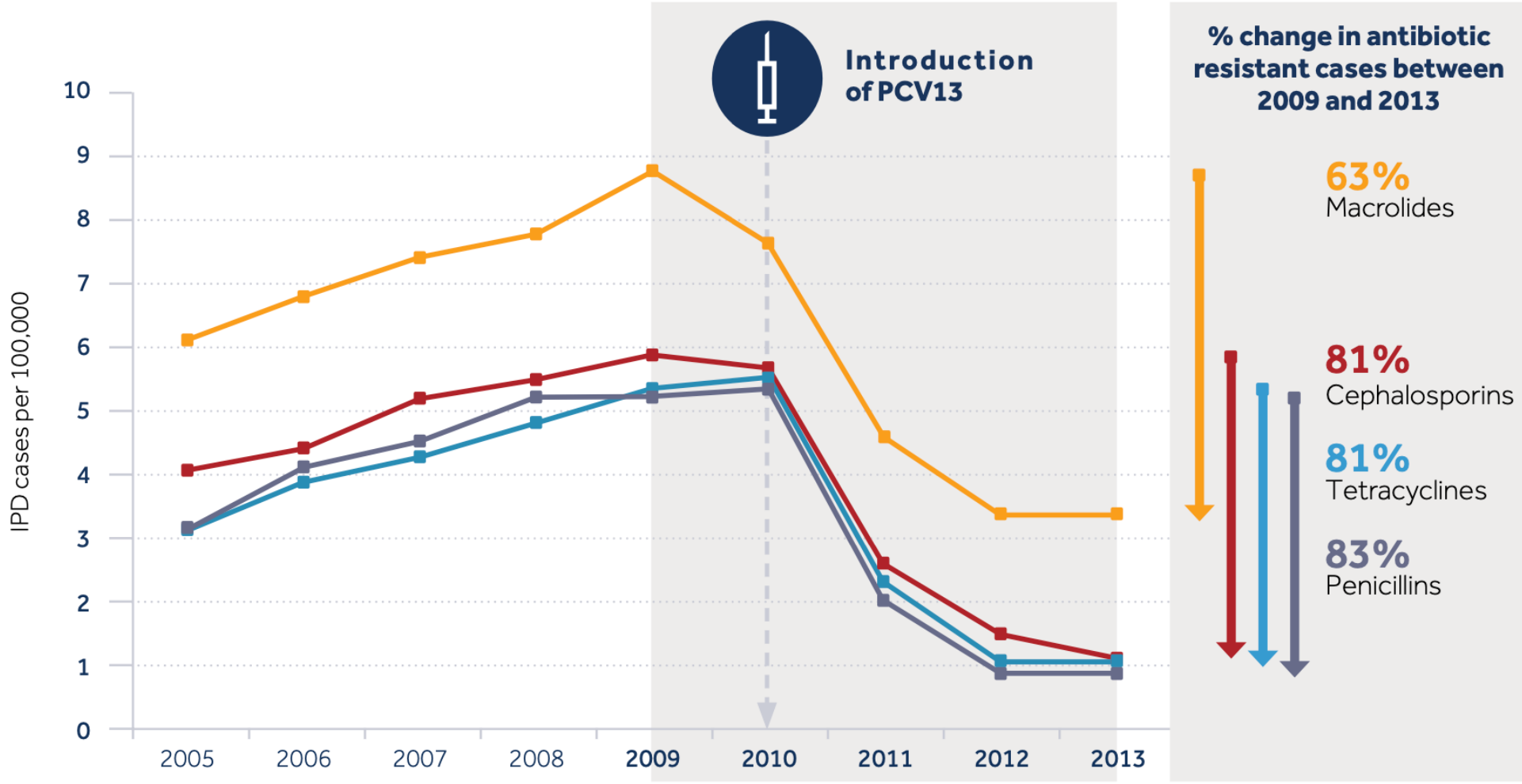
Introduction of PCV13
IPD cases per 100,000
10
9
8
7
6
5
4
3
2
1
0
2005
2006
2007
2008
2009
2010
2011
2012
2013
% change in antibiotic resistant cases between 2009 and 2013
63%
Macrolides
81%
Cephalosporins
81%
Tetracyclines
83%
Penicillins

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* Nessuna attività antibatterica diretta
* Prevenzione virosi con conseguente riduzione prescrittiva di antibiotici inutili
* Prevenzione di sovrainfezioni batteriche in corso di malattie virali

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Influenza e riduzione AMR


REVIEW

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* In the U.S., nearly half of all antibiotic prescriptions are written for respiratory illnesses associated with pathogens such as influenza that are not susceptible to antibiotics
* In Ontario, Canada, universal influenza vaccination resulted in approximately 64% reduction in influenza-associated antibiotic prescriptions (Kwong et al. 2009)
* In the UK, children 2–4 years of age who were vaccinated with a live-attenuated influenza vaccine had 14.5% fewer amoxicillin prescriptions during the period of influenza vaccine immunity compared with other winter seasons (Hardelid et al. 2018).

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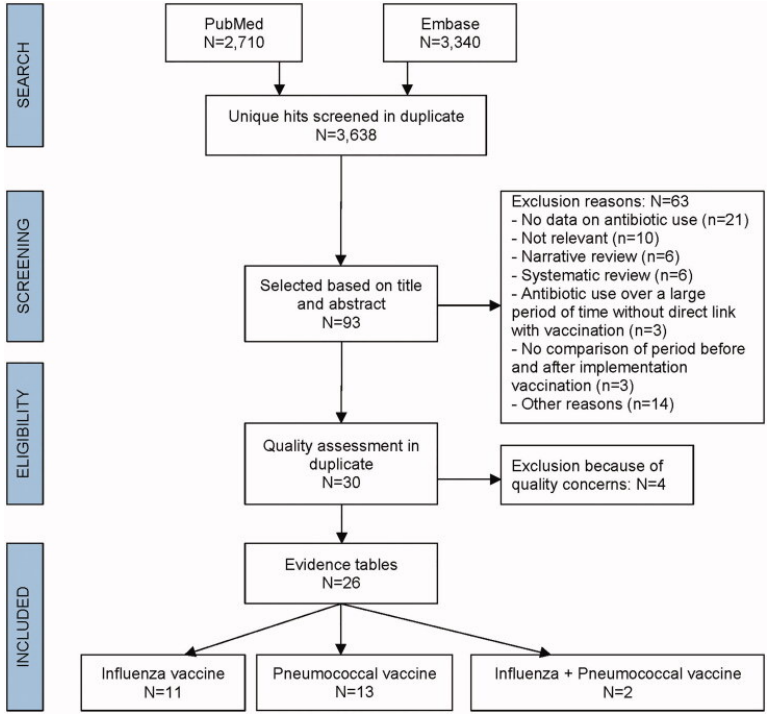
Review

Specific and Nonspecific Effects of Influenza Vaccines

Nicola Principi [1] and Susanna Esposito [2,*]

* A reduction in antibiotic prescriptions in individuals given influenza vaccine is clearly evidenced in a recent systematic review and meta-analysis of 26 studies
* influenza vaccine use is associated with both the reduction in the proportion of people receiving antibiotics (RR 0.63, 95% confidence interval [CI] 0.51–0.79) and the reduction in number of antimicrobial prescriptions or days of antibiotic use (RR 0.71, 95% CI 0.62–0.83)



Moreover, there are data that seem to confirm that influenza vaccines can reduce the risk of superimposed bacterial infections and, consequently, the number of antibiotic prescriptions.

Vaccines **2024**, *12*, 384. https://doi.org/10.3390/vaccines12040384

Efficacy of Injectable Trivalent Virosomal-Adjuvanted Inactivated Influenza Vaccine in Preventing Acute Otitis Media in Children With Recurrent Complicated or Noncomplicated Acute Otitis Media

Methods: In this prospective, randomized, single-blinded, placebo-controlled study, 180 children aged 1 to 5 years with a history of rAOM and previously unvaccinated against influenza were randomized to receive the inactivated virosomal-adjuvanted subunit influenza vaccine (n = 90) or no treatment (n = 90), and AOM-related morbidity was monitored every 4 to 6 weeks for 6 months.

Results: The number of children experiencing at least 1 AOM episode was significantly smaller in the vaccinated group ($P < 0.001$), as was the mean number of AOM episodes ($P = 0.03$), the mean number of AOM episodes without perforation ($P < 0.001$), and the mean number of antibiotic courses ($P < 0.001$); the mean duration of bilateral OME was significantly shorter ($P = 0.03$). The only factor that seemed to be associated with the significantly greater efficacy of influenza vaccine in preventing AOM was the absence of a history of recurrent perforation (crude odds ratio, $P = 0.01$; adjusted odds ratio, $P = 0.006$).

Conclusions: The intramuscular administration of injectable trivalent inactivated virosomal-adjuvanted influenza vaccine in children with a history of rAOM significantly reduces AOM-related morbidity. However, the efficacy of this preventive measure seems to be reduced in children with rAOM associated with repeated tympanic membrane perforation.

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2022, VOL. 18, NO. 7, e2151291 (8 pages)
https://doi.org/10.1080/21645515.2022.2151291

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REVIEW

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Available evidence and potential for vaccines for reduction in antibiotic prescriptions

Giovanni Gabutti

Coordinator Working Group, Vaccines and Immunization Policies of the Italian Scientific Society of Hygiene, Preventive Medicine and Public Health (SItI), Cogorno (Ge), Italy

* A study conducted in 3 areas of the USA estimated the incidence of physician-assisted influenza cases and cases avoided with vaccination for the influenza seasons from 2013/14 to 2015/16. The incidence of influenza with medical assistance was between 14 and 54 per 1,000 population while the cases avoided ranged from 9 (2014/15 season) to 28 per 1,000 (2013/14 season) indicating that the vaccination schedule involved significant reductions in outpatient visits for influenza, even in years when vaccine was not well matched to the dominant circulating influenza strain. It has been shown that on average, vaccinating 1,000 people avoided 13.9 outpatient visits due to influenza; in practice, 1 outpatient visit was avoided for every 72 immunized subjects

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* The assessment of the impact of influenza vaccination in the 2016/2017 season in the USA showed that vaccination coverage rates ranged from 33% (Nevada) to 52% (Rhode Island), while antibiotic use rates ranged from 125 (Alaska) to 377 prescriptions per 1,000 population (West Virginia). In particular, vaccination coverage rates were highly correlated with reduced prescription rates; a 1% increase in influenza vaccination rate was significantly associated with 1.40 fewer antibiotic prescriptions per 1,000 population. The increased vaccination coverage rate in the pediatric population (ages 0–18 years) had the strongest effect, followed by that observed in the elderly (>65 years)

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* The potential impact of influenza vaccination on antibiotic use has also been assessed in Africa. It is estimated that the direct impact of vaccination could avoid more than 390 prescriptions per 100,000 population per year by using a 50% effective influenza vaccine with 30% coverage in adults >65 years of age in South Africa or in children aged between 2 and 5 years in Senegal. Across Africa, simply by reducing the number of severe acute respiratory infections, the use of a vaccine with the same characteristics could avoid at least 24,000 antibiotic prescriptions per year if administered to children <5 years of age

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* a synergistic effect exerted by the pneumococcal and influenza vaccines can be postulated. A meta-analysis showed that the additional preventive effects of the concomitant vaccination (influenza and pneumococcal vaccines) compared to influenza vaccination alone for pneumonia and death were 15% and 19%, respectively. Compared to pneumococcal vaccination alone, concomitant influenza and pneumococcal vaccination resulted in a 24% reduction in pneumonia and 28% reduction in death; when compared with placebo or no vaccination, the efficacy of concomitant vaccination was 29% for pneumonia, 38% for death, 35% for influenza, and 18% for hospitalization.

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Clinical Infectious Diseases

MAJOR ARTICLE

Reducing Antibiotic Use in Ambulatory Care Through Influenza Vaccination

Emily R. Smith,[1,©] Alicia M. Fry,[1] Lauri A. Hicks,[1] Katherine E. Fleming-Dutra,[1] Brendan Flannery,[1] Jill Ferdinands,[1] Melissa A. Rolfes,[1] Emily T. Martin,[2] Arnold S. Monto,[2] Richard K. Zimmerman,[3] Mary Patricia Nowalk,[3] Michael L. Jackson,[4] Huong Q. McLean,[5] Scott C. Olson,[5] Manjusha Gaglani,[6] and Manish M. Patel[1]

[1]Centers for Disease Control and Prevention, Atlanta, Georgia, USA, [2]University of Michigan, Ann Arbor, Michigan, USA, [3]University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA, [4]Kaiser Permanente Washington Health Research Institute, Seattle, Washington, USA, [5]Marshfield Clinic Research Institute, Marshfield, Wisconsin, USA, and [6]Baylor Scott & White Health, Texas A&M University, Temple, Texas, USA

Background. Improving appropriate antibiotic use is crucial for combating antibiotic resistance and unnecessary adverse drug reactions. Acute respiratory illness (ARI) commonly causes outpatient visits and accounts for ~41% of antibiotics used in the United States. We examined the influence of influenza vaccination on reducing antibiotic prescriptions among outpatients with ARI.

Methods. We enrolled outpatients aged ≥6 months with ARI from 50–60 US clinics during 5 winters (2013–2018) and tested for influenza with RT-PCR; results were unavailable for clinical decision making and clinical influenza testing was infrequent. We collected antibiotic prescriptions and diagnosis codes for ARI syndromes. We calculated vaccine effectiveness (VE) by comparing vaccination odds among influenza-positive cases with test-negative controls. We estimated ARI visits and antibiotic prescriptions averted by influenza vaccination using estimates of VE, coverage, and prevalence of antibiotic prescriptions and influenza.

Results. Among 37 487 ARI outpatients, 9659 (26%) were influenza positive. Overall, 36% of ARI and 26% of influenza-positive patients were prescribed antibiotics. The top 3 prevalent ARI syndromes included: viral upper respiratory tract infection (47%), pharyngitis (18%), and allergy or asthma (11%). Among patients testing positive for influenza, 77% did not receive an ICD-CM diagnostic code for influenza. Overall, VE against influenza-associated ARI was 35% (95% CI, 32–39%). Vaccination prevented 5.6% of all ARI syndromes, ranging from 2.8% (sinusitis) to 11% (clinical influenza). Influenza vaccination averted 1 in 25 (3.8%; 95% CI, 3.6–4.1%) antibiotic prescriptions among ARI outpatients during influenza seasons.

Conclusions. Vaccination and accurate influenza diagnosis may curb unnecessary antibiotic use and reduce the global threat of antibiotic resistance.

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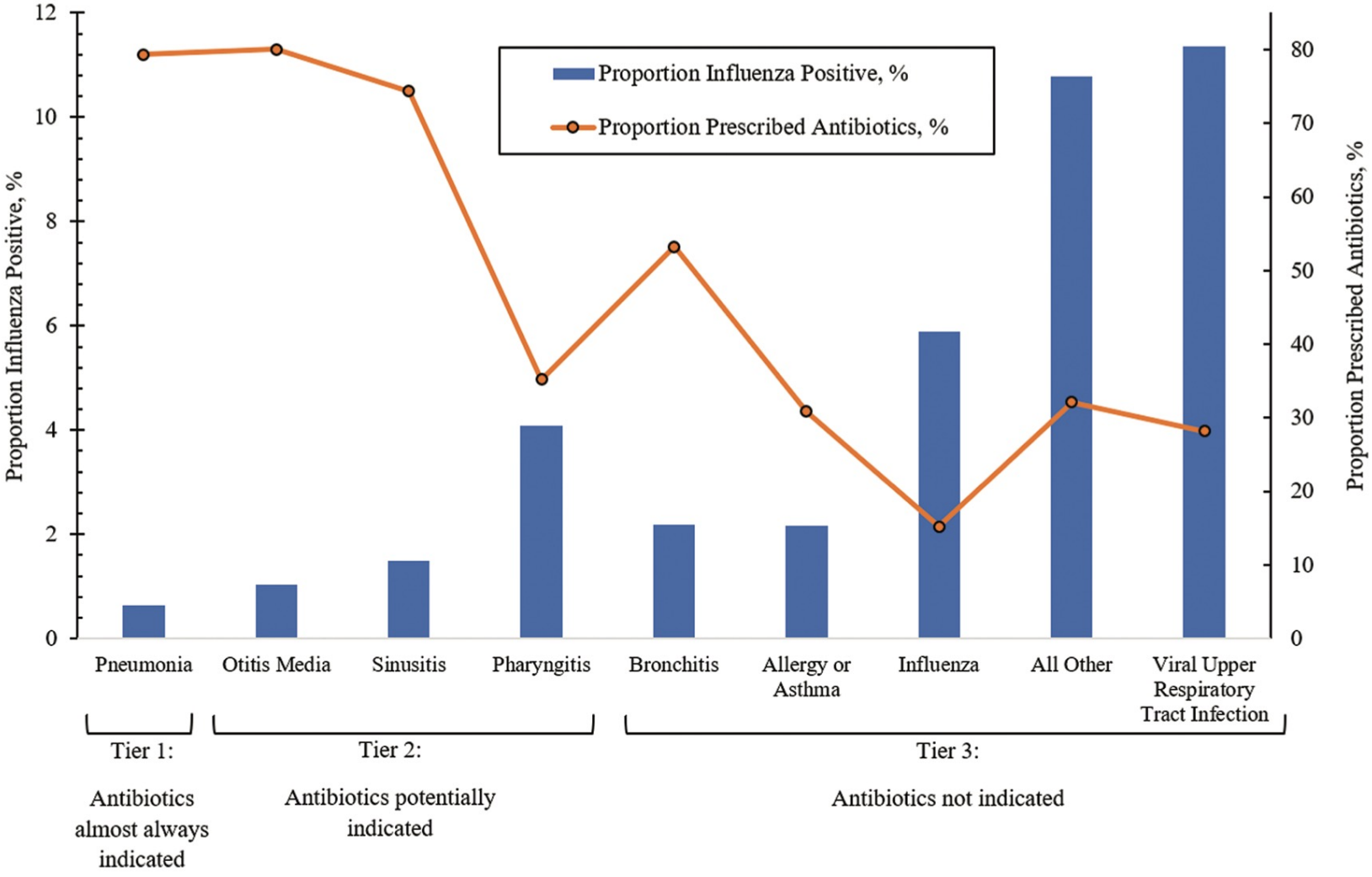

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ANNALS OF MEDICINE
2020, VOL. 52, NO. 6, 283–299
https://doi.org/10.1080/07853890.2020.1782460

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ORIGINAL ARTICLE

Effect of vaccination on the use of antimicrobial agents: a systematic literature review

T. Mark Doherty[a], William P. Hausdorff[b,c] and Karl G. Kristinsson[d,e]

ABSTRACT

Background: Antimicrobial resistance is a growing global health threat. To preserve the effectiveness of antimicrobials, it is important to reduce demand for antimicrobials.

Objectives: The objective of the study was to screen the existing peer-reviewed literature to identify articles that addressed the potential impact of influenza or *Pneumococcus* vaccination on antibiotic usage.

Data sources: PubMed, Embase

Study eligibility criteria: Clinical studies where antimicrobial prescribing was assessed in both vaccinated and unvaccinated populations.

Participants and interventions: All patient populations were included (infants, children, adults and elderly), where the effects of the intervention (vaccination) was assessed

Results: We identified unique 3638 publications, of which 26 were judged to be of sufficiently high quality to allow the calculation of the potential impact of vaccination. Of these studies 23/26 found a significant reduction in antibiotic use by at least one of the parameters assessed.

Limitations: Different measures used to define anti-microbial use, studies typically focus on specific risk groups and most studies are from high-income countries.

Conclusions and implications of key findings: Despite the limitations of the review, the evidence indicates that improved coverage with existing vaccines may significantly reduce antimicrobial demand. This suggests it may be a valuable tool for antimicrobial stewardship.

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ORIGINAL ARTICLE

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Effect of vaccination on the use of antimicrobial agents: a systematic literature review

T. Mark Doherty[a], William P. Hausdorff[b,c] and Karl G. Kristinsson[d,e]

Table 2. Influenza vaccination studies examining antimicrobial use in children.

Reference (SIGN)	Design	Population	N*	Mean age (range)*	Influenza Season	Outcome description	Outcome			Direction effect (−, −/+, +)
							Measure	Outcome	95% CI/*p*-value	
Esposito (++) [17]	RCT	Children	64/63	3.8 yrs (6 mo–14 yrs)	2000–2001	Antimicrobial prescriptions for URI	VE	44%	<.0001	+
Marchisio (+) [23]	RCT	Children	90/90	2.1/2.2 yrs (1–5 yrs)	2006–2007	Antimicrobial courses	VE	13.2%	<.001	+
Salleras (+) [27]	Non-randomized	Children	1951	NR (3–14 yrs)	2004–2005	Antimicrobial consumption	VE	18.6%	−4.2%−36.4%	−/+
Hardelid (o) [34]	Self-controlled case series	Children	15,543	NR (2–3 yrs)	2013–2014	Amoxicillin prescriptions	VE	12.6%	6.7%−18.2%	+
			22,665	NR (2–4 yrs)	2014–2015	Amoxicillin prescriptions	VE	14.5%	9.6%−19.2%	+

*Vaccinated/unvaccinated; CI: confidence interval; mo: months; NR: not reported; RCT: randomized controlled trial; SIGN: Scottish Intercollegiate Guidelines Network; URI: upper respiratory infection; URI: upper respiratory infection; VE: vaccine effectiveness; yrs: years.

Table 4. Influenza vaccination studies examining transmission within households.

Reference (SIGN)	Design	Population	*N*	Mean age (range)* in years	Season	Outcome description	Outcome			Direction effect (−, −/+, +)
							Measure	Outcome	95% CI/ *p*-value	
Antimicrobial use of household contacts of vaccinated children										
Esposito (++) [17]	RCT	Parents	254	36.8/38.1	2000–2001	Antimicrobial prescriptions	VE	27%	.01	+
		Siblings	95	5.3/5.0	2000–2001	Antimicrobial prescriptions	VE	33%	.01	+
Hurwitz (+) [24]	RCT	Household contacts	29	0–4	1996–1997	Antimicrobial prescriptions	VE	NR		−/+
			59	5–17	1996–1997	Antimicrobial prescriptions	VE	88%	.02	+
			140	≥18	1996–1997	Antimicrobial prescriptions	VE	NR		−/+
Vaccination of household contacts and antimicrobial use in infants										
Maltezou (++) [21]	Non-randomized	Mother–infant	530	30.5 (15–46)/ 30.9 (15–45)	2012–2013	Antimicrobial administration	Difference**	45.4%	.014	+
					2012–2013	Antimicrobial administration	OR***	0.472	0.911–0.245/.025	+
		Other household contacts	1291*	NR	2012–2013	Antimicrobial administration	NR		NS	−/+

* Overall, there were 1844 members in the 553 studied households, including 553 mothers, 525 fathers, 358 siblings, 323 grandparents, 73 other relatives, and 12 caregivers; ** Number of antimicrobial administrations (95% CI) in infants of vaccinated mothers: 22 (4.9–11.6) *versus* infants of unvaccinated mothers: 40 (10.8–19.5);*** The odds ratio is presented here has been calculated in conventional format as the risk in post-partum vaccinated mothers, rather than the original format which presented the risk in those unvaccinated; CI confidence interval; NR: not reported; NS: not significant; OR: odds ratio; RCT: randomized controlled trial; SIGN: Scottish Intercollegiate Guidelines Network; VE: vaccine effectiveness.

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Tuttavia …

Effect of Pediatric Influenza Vaccination on Antibiotic Resistance, England and Wales

Chungman Chae,[1] Nicholas G. Davies,[1] Mark Jit, Katherine E. Atkins

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 26, No. 1, January 2020

Vaccines against viral infections have been proposed to reduce prescribing of antibiotics and thereby help control resistant bacterial infections. However, by combining published data sources, we predict that pediatric live attenuated influenza vaccination in England and Wales will not substantially reduce antibiotic consumption or adverse health outcomes associated with antibiotic resistance.

Table 1. Projected effect of pediatric LAIV on antibiotic prescription rates, England and Wales*

Age group	Influenza-attributed consultation rate†	Prescriptions per consultation	Direct prescribing rate reduction, unmatched‡	Direct prescribing rate reduction, matched‡	Overall LAIV effectiveness§	Overall prescribing rate reduction¶
0–6 mo	29.7 (23.7–35.9)	0.597 (0.474–0.719)	–	–	0.574 (0.501–0.651)	10.2 (7.03–13.5)
6 m–4 y	29.7 (23.7–35.9)	0.597 (0.474–0.719)	7.46 (5.31–9.64)	12.4 (8.85–16.1)	0.663 (0.618–0.714)	11.8 (8.31–15.4)
5–14 y	22.1 (17.6–26.7)	0.588 (0.466–0.708)	5.46 (3.89–7.06)	9.11 (6.48–11.8)	0.754 (0.709–0.794)	9.81 (6.97–12.8)
15–44 y	12.8 (10.2–15.4)	0.676 (0.536–0.814)	3.64 (2.59–4.70)	6.06 (4.31–7.83)	0.446 (0.394–0.502)	3.86 (2.66–5.09)
45–64 y	12.4 (9.84–14.9)	0.805 (0.639–0.970)	–	–	0.423 (0.374–0.484)	4.22 (2.90–5.58)
≥65 y	12.2 (9.67–14.7)	0.857 (0.680–1.03)	–	–	0.477 (0.397–0.561)	4.97 (3.34–6.68)
Overall	14.7 (11.7–17.7)	0.726 (0.576–0.875)	5.80 (4.13–7.49)	9.86 (7.01–12.9)	0.494 (0.446–0.549)	5.32 (3.74–7.00)

*All estimates reported as mean (95% highest density interval). LAIV, live attenuated influenza vaccine; –, age group not subject to pediatric LAIV.
†Per 1,000 person-years in England and Wales.
‡Reduction in antibiotic prescriptions among vaccinees per 1,000 vaccine recipients, not accounting for herd immunity, presented separately for unmatched and matched seasons.
§Reduction in influenza cases assuming a 50% uptake among children 2–16 years of age, accounting for herd immunity.
¶Per 1,000 person-years in England and Wales, accounting for herd immunity.

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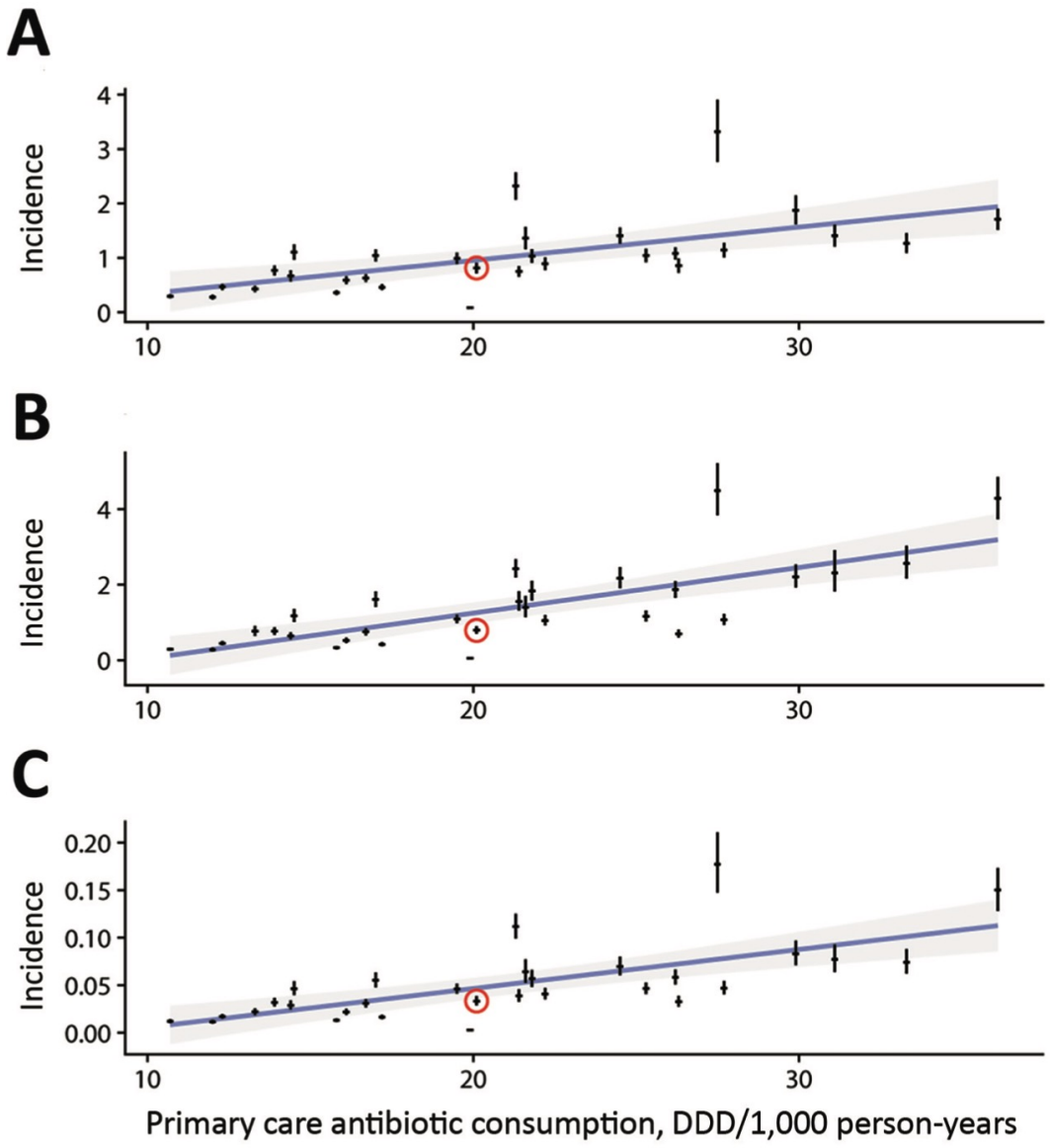

Figure 1. Estimated incidence of adverse health outcomes resulting from antibiotic-resistant infections, plotted against the overall antibiotic consumption in primary care settings in 30 countries in Europe, 2015. A) Antibiotic-resistant cases/1,000-person-years; B) attributable DALYs/1,000 person-years; C) attributable deaths/1,000 person-years. Red circles indicate datapoints for the United Kingdom; error bars indicate 95% CIs. Blue lines indicate linear regressions; gray shading indicates 95% confidence regions for linear regressions. DALYs, disability-adjusted life years; DDD, defined daily dose.

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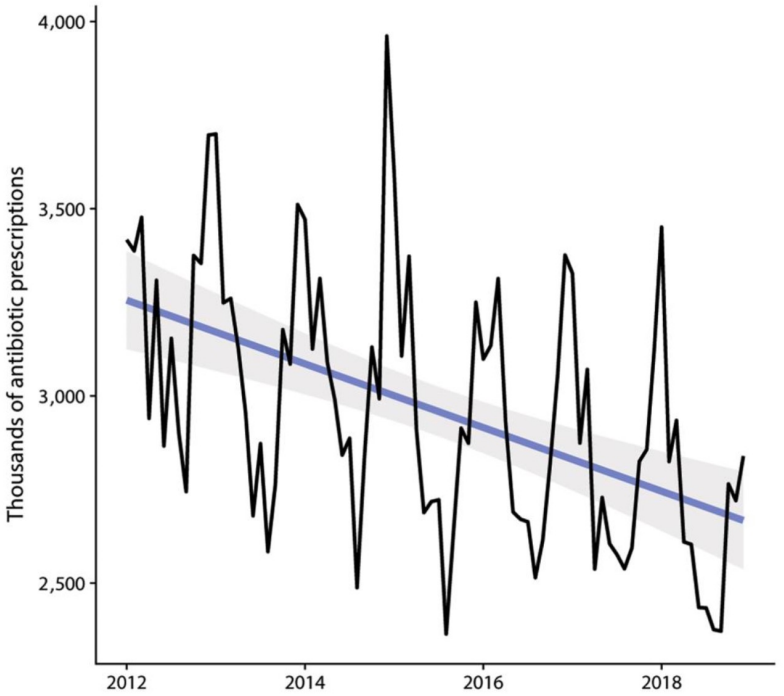
- Our estimates for the foreseeable reduction in antibiotic prescribing from the LAIV program in England and Wales might seem surprisingly low, given that sore throat, cough, and sinusitis together account for 53% of all inappropriate prescribing, which in turn accounts for at least 9%–23% of all prescribing in England
- influenza causes only 11% of GP consultations for acute respiratory illness in England, so it might be optimistic to expect influenza vaccination to substantially reduce antibiotic use in this setting



Appendix Figure. Antibiotic use in England has fallen by ≈2.5% each year from 2012 to 2018.

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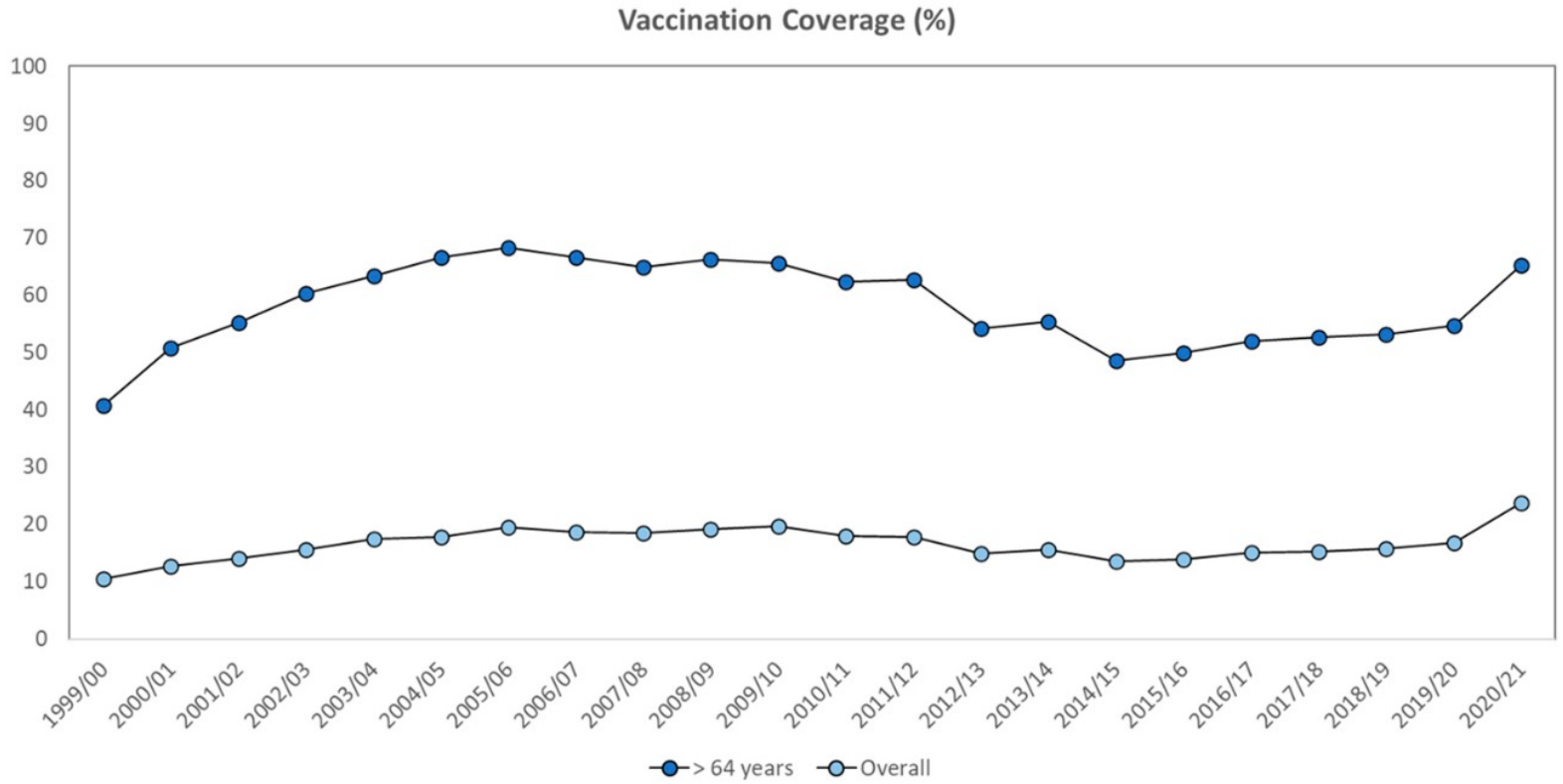
The Inverse Relationship between Influenza Vaccination and Antimicrobial Resistance: An Ecological Analysis of Italian Data

Martina Barchitta, Andrea Maugeri, Rosario Vinci and Antonella Agodi *

https://www.mdpi.com/journal/vaccines

Vaccines **2022**, *10*, 554. https://doi.org/10.3390/vaccines10040554



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Species	Annual Number of Isolates Tested	Antimicrobials	Period	% Resistance		
				Mean	SD	Range
A. baumannii	236–2522	Aminoglycosides	2012–2020	79.6	4.3	74.7–88.3
		Carbapenems	2012–2020	80.8	3.7	78.3–89.9
		Fluoroquinolones	2012–2020	83.2	3.9	79.2–92.1
E. coli	564–7533	Fluoroquinolones	2002–2020	36.6	7.5	21.1–44.9
		3rd gen. Cephalosporins	2002–2020	19.6	9.9	2.9–30.9
		Aminoglycosides	2002–2020	15.1	4.7	5.9–22.3
		Aminopenicillins	2002–2020	61.9	6.2	48.0–68.1
K. pneumoniae	305–8293	Carbapenems	2006–2020	21.7	13.5	1.1–34.3
		3rd gen. Cephalosporins	2005–2020	46.7	11.1	19.5–57.6
		Aminoglycosides	2005–2020	28.9	7.7	7.9–37.0
		Fluoroquinolones	2005–2020	42.4	15.3	11.3–56.1
S. aureus	470–10923	Methicillin	2000–2020	36.5	3.0	33.5–44.3
P. aeruginosa	151–4537	Fluoroquinolones	2006–2020	28.9	6.3	19.6–42.0
		Piperacillin and tazobactam	2006–2020	23.1	5.4	13.3–30.6
		Carbapenems	2006–2020	22.8	5.3	13.7–32.9
		Ceftazidime	2006–2020	21.1	3.2	16.2–25.5
S. pneumoniae	141–1017	Penicillins	2005–2020	4.1	1.9	0.8–8.6
		Macrolides	2005–2020	25.2	3.8	19.4–33.8

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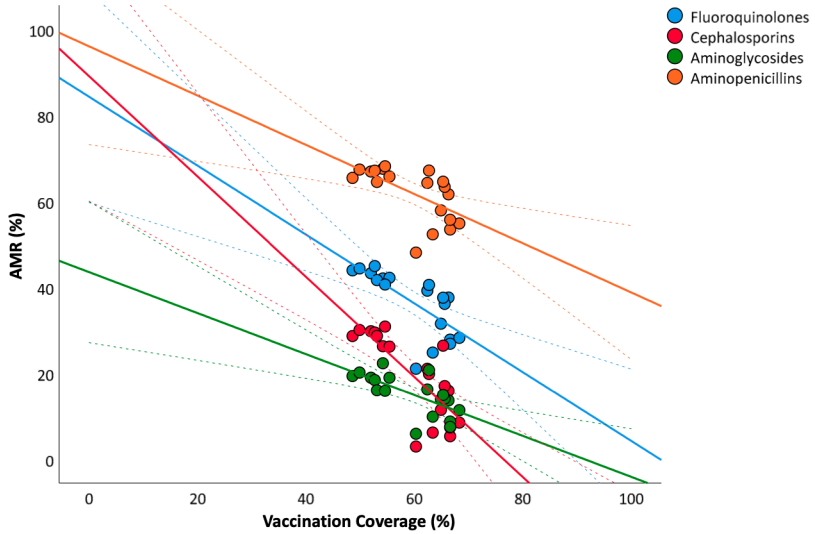

Figure 3. The relationship between influenza vaccination coverage in population over 64 years and antimicrobial resistance of *Escherichia coli*. The plot shows linear regression lines and their 95%CI (dotted lines).

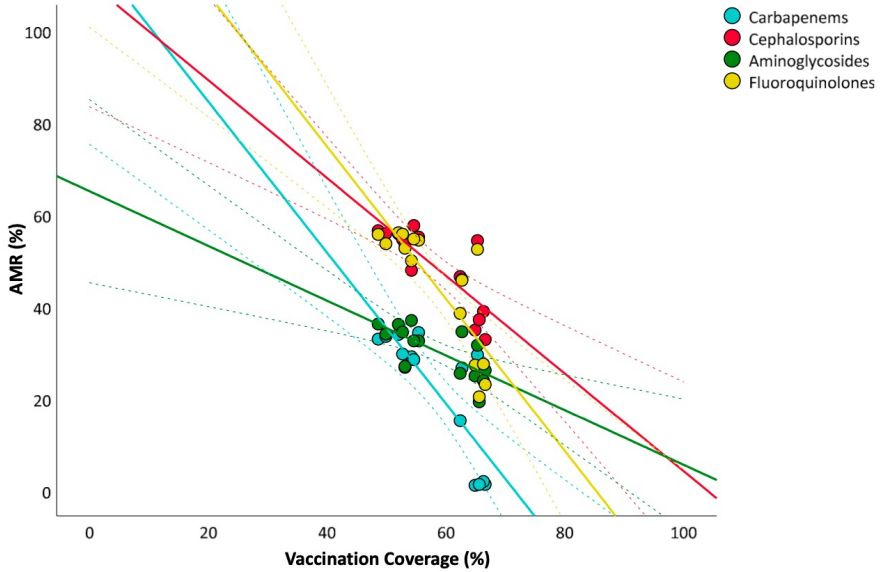

Figure 4. The relationship between influenza vaccination coverage in population over 64 years and antimicrobial resistance of *Klebsiella pneumoniae*. The plot shows linear regression lines and their 95% CI (dotted lines).

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Slide già vista

* Molte nazioni hanno introdotto il vaccino antinfluenzale nella schedula vaccinale ufficiale, ed i dati epidemiologici confermano efficacia, tollerabilità e netta riduzione dei casi annuali di influenza e complicanze
* Tali studi evidenziano anche come la vaccinazione antinfluenzale possa controllare l'antibiotico resistenza (AMR)
* Inoltre altri studi suggeriscono che la vaccinazione antinfluenzale potrebbe avere effetti non specifici (NSEs), creando cioè protezione verso infezioni non coperte da vaccino modulando l'incidenza e il decorso di alcune patologie immuno - mediate

Vaccines **2024**, *12*, 384. https://doi.org/10.3390/vaccines12040384

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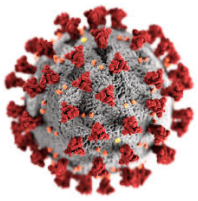
Vaccine

Do vaccines increase or decrease susceptibility to diseases other than those they protect against?

Alberto Rubio-Casillas [a,b], Cesar Manuel Rodriguez-Quintero [b], Elrashdy M. Redwan [c,d], Munishwar Nath Gupta [e,1], Vladimir N. Uversky [f,*], Mikolaj Raszek [g]

Contrary to the long-held belief that the effects of vaccines are specific for the disease they were created; compelling evidence has demonstrated that vaccines can exert positive or deleterious non-specific effects (NSEs). In this review, we compiled research reports from the last 40 years, which were found based on the PubMed search for the epidemiological and immunological studies on the non-specific effects (NSEs) of the most common human vaccines. Analysis of information showed that live vaccines induce positive NSEs, whereas non-live vaccines induce several negative NSEs, including increased female mortality associated with enhanced susceptibility to other infectious diseases, especially in developing countries. These negative NSEs are determined by the vaccination sequence, the antigen concentration in vaccines, the type of vaccine used (live vs. non-live), and also by repeated vaccination. We do not recommend stopping using non-live vaccines, as they have demonstrated to protect against their target disease, so the suggestion is that their detrimental NSEs can be minimized simply by changing the current vaccination sequence. High IgG4 antibody levels generated in response to repeated inoculation with mRNA COVID-19 vaccines could be associated with a higher mortality rate from unrelated diseases and infections by suppressing the immune system. Since most COVID-19 vaccinated countries are reporting high percentages of excess mortality not directly attributable to deaths from such disease, the NSEs of mRNA vaccines on overall mortality should be studied in depth.

Vaccine 42 (2024) 426–440



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* Vaccination may have an impact on illnesses that it is not intended to protect
* cross reactivity: cowpox and smallpox
* even vaccines turn out to be non-specific in the sense of influencing immune responses of the diseases for which they were not designed
* these non-specific effects are not based upon cross-reactivity of antibodies
* they are seen in diseases which are, unlike cowpox and smallpox, quite unrelated

Vaccine 42 (2024) 426–440

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Review

Specific and Nonspecific Effects of Influenza Vaccines

Nicola Principi [1] and Susanna Esposito [2,*]

Type of Effect and Vaccine	Nonspecific Effects
Positive	
Bacillus Calmette-Guerin (BCG) vaccine	Reduced mortality within the neonatal period or by age of 12 months; protection against malignancies, allergy, and autoimmune diseases, including type 1 diabetes
Measles vaccine	Reduction in global pediatric mortality, with girls showing the greatest benefit
Smallpox	Reduction in global pediatric mortality
Live poliovirus vaccine (OPV)	Reduction in gastrointestinal infections in Latin America, of respiratory infections in Russia, and of global child mortality in several underdeveloped countries
Negative	
Diphtheria-tetanus-pertussis (DTP) vaccine	Increased deaths from other diseases than it prevents from the target infections when is given after live vaccines
Inactivated polio vaccine (IPV)	Increase all-cause mortality by 10%
Malaria vaccine RTS,S/AS01	Increase in all-cause mortality in girls
Hepatitis B vaccine (HBV)	Increase in mortality with the difference being particularly strong for girls

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NSE and influenza

Do vaccines increase or decrease susceptibility to diseases other than those they protect against?

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* 2009, Mexico. H1N1 Outbreak and pandemic diffusion children who received the H1N1 vaccine would consult with doctors more frequently than children who did not receive the vaccine, despite having immunity to the H1N1 influenza
* the non-live H1N1 vaccine, along with other non-live vaccines, could render children more susceptible to other infectious diseases
* no evidence that a possibly detrimental outcome of H1N1 was greatest for females
* impact of H1N1 influenza vaccines on overall mortality has not been thoroughly studied

Vaccine 42 (2024) 426–440

NSE and influenza

Type of Vaccine	Nonspecific Effects
Live attenuated influenza vaccine (LAIV)	Some data on the reduction in the total number of non-influenza medical attended respiratory infections in both children and adults
	Nonspecific cross-protection against respiratory syncytial virus, suggesting a remodulation of innate immune activity
Inactivated influenza vaccine (IIV)	Conflicting results on the incidence of non-influenza respiratory infections
	Significant protective effect of 4IIV against COVID-19
	Reduction in RSV hospitalizations in children, especially in those <2 years, with 4IIVs
	Reduced risk of developing or worsening coronary heart disease and heart failure; no effect on stroke
	Potential protective effect of influenza vaccine in development and progression of type 1 diabetes (T1D), cancer, and Alzheimer's disease
	Conflicting results on epigenetic and transcriptional reprogramming as well as cytokine responses of immune cells after administration

NSE: conclusions

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* Nonspecific effects were mainly due to a previously unknown mechanism that is the development of innate immune memory, also named trained immunity, although a role is supposed to be played by the heterologous T-cell immunity also
* Recognizing that non-live vaccines have negative effects does not mean that they should stop being used, and should not encourage people who believe that vaccines only cause harm to continue to refuse them. Like any medicine, non-live vaccines can in some circumstances induce iatrogenic effects, which can be effectively neutralized when the last to be applied is a live vaccine

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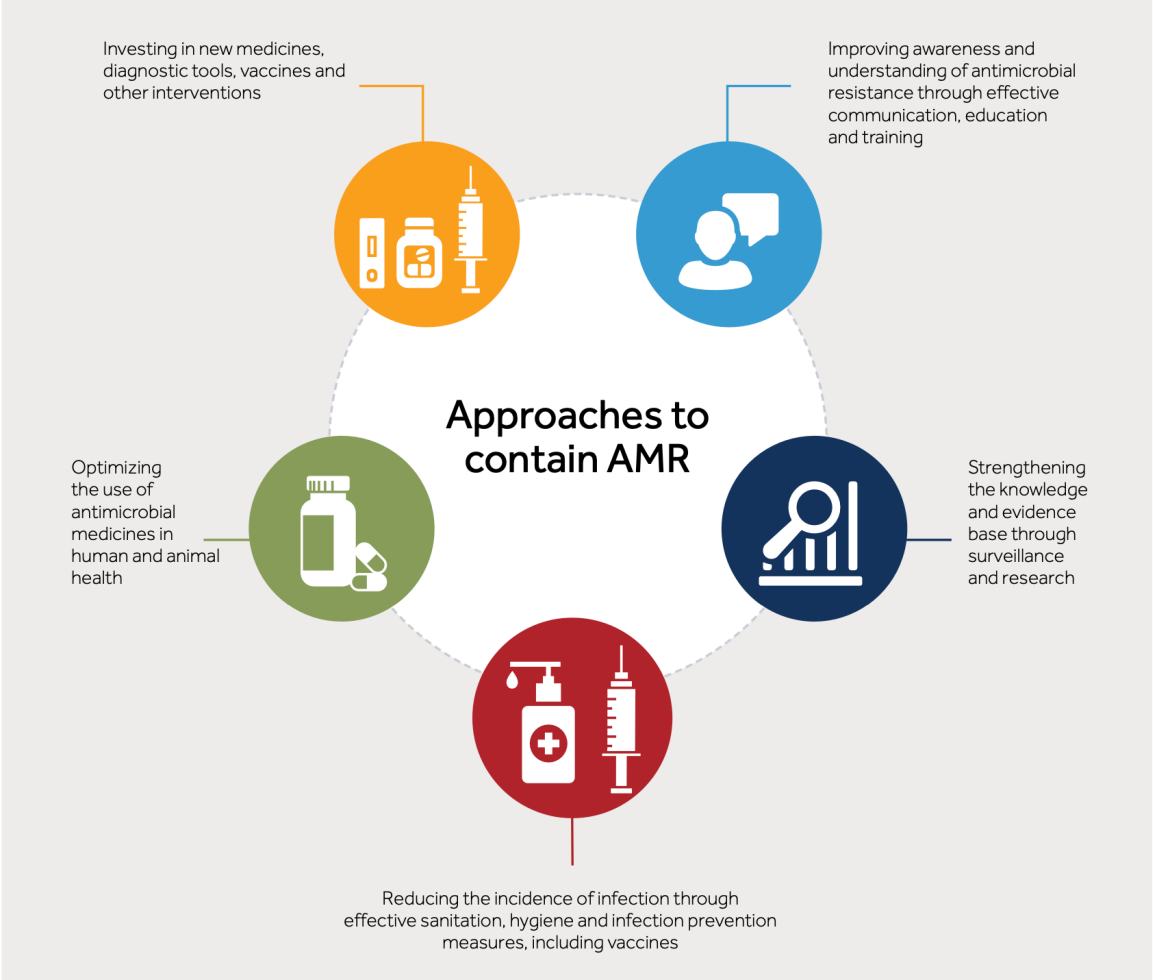
A global strategy to leave no one behind

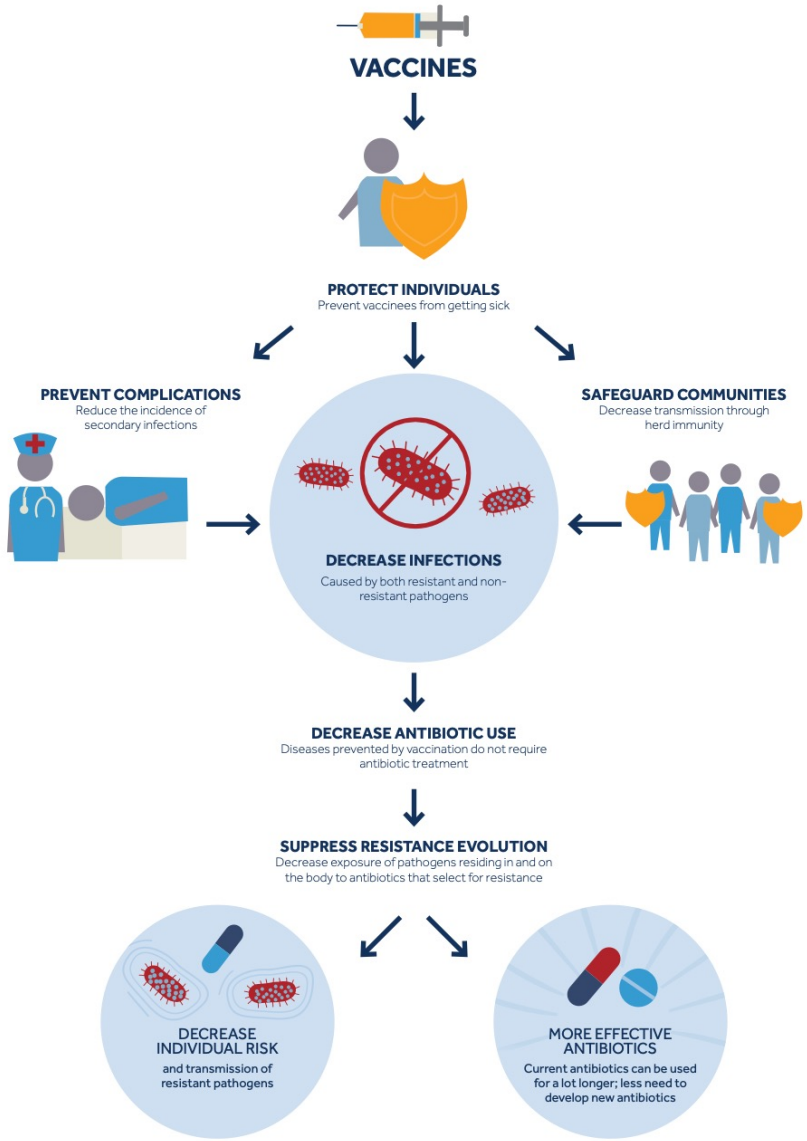


Annex to Immunization Agenda 2030

Leveraging Vaccines to Reduce Antibiotic Use and Prevent Antimicrobial Resistance:

An Action Framework

World Health Organization


VACCINES
PROTECT INDIVIDUALS
Prevent vaccinees from getting sick
PREVENT COMPLICATIONS
Reduce the incidence of secondary infections
SAFEGUARD COMMUNITIES
Decrease transmission through herd immunity
DECREASE INFECTIONS
Caused by both resistant and non-resistant pathogens
DECREASE ANTIBIOTIC USE
Diseases prevented by vaccination do not require antibiotic treatment
SUPPRESS RESISTANCE EVOLUTION
Decrease exposure of pathogens residing in and on the body to antibiotics that select for resistance
DECREASE INDIVIDUAL RISK
and transmission of resistant pathogens
MORE EFFECTIVE ANTIBIOTICS
Current antibiotics can be used for a lot longer; less need to develop new antibiotics

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Annex to Immunization Agenda 2030

Leveraging Vaccines to Reduce Antibiotic Use and Prevent Antimicrobial Resistance:

An Action Framework

GOAL
Expand use of licensed vaccines to maximize impact on AMR

OBJECTIVES	ACTIONS	AUDIENCE
1 Increase coverage of vaccines with impact on AMR.	**1a.** Countries should implement existing vaccine-related recommendations of the Global Action Plan on AMR.	
	1b. Donors, countries and other health payers should maintain and expand immunization financing and strengthen capacities, ensuring affordable supply, functional delivery systems and programmatic sustainability.	
2 Update recommendations and normative guidance in both the vaccine and AMR sectors to include the role of vaccines to control AMR.	**2a.** Where justified, normative guidance, regulatory indications, policy recommendations and health regulations for vaccine use should be adapted to account specifically for the use of vaccines to impact AMR.	
	2b. AMR national action plans and international organizations dedicated to AMR control should consistently include vaccines in the armamentarium of interventions planned for use against AMR, and build capacity for the full realization of vaccine impact as individual or combined interventions.	
	2c. Immunization programmes should be strengthened to reach children beyond the first year of life, and immunization services broadened to support vaccination with impact on AMR throughout the life course.	
	2d. In a "One Health" perspective, bodies such as the Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE) and the World Health Organization (WHO), in collaboration with the agricultural industry and animal health stakeholders, should update recommendations and regulations and develop an action plan to maximize the use of animal vaccines to reduce antibiotic use in animals.	
3 Improve awareness and understanding of the role of vaccines in limiting AMR through effective communication, education and training.	**3a.** Countries, funders and other stakeholders should include the role of vaccines in limiting AMR in communication materials used to present their related activities.	
	3b. Institutions involved in the vaccine and AMR sectors should develop communication, education and training materials about the role of vaccines in controlling AMR, targeting audiences ranging from the general public to infectious disease experts.	

Key:

- governments, national immunization technical advisory groups, and agencies
- health-care workers, professional medical associations, patient groups, civil society and subnational organizations
- regulators and policy-makers
- the pharmaceutical industry
- academic researchers
- funders of research
- media and educators
- the agricultural and animal industry sectors
- public health advocates

GOAL
Develop new vaccines that contribute to prevention and control of AMR

OBJECTIVES	ACTIONS	AUDIENCE
4 Bridge the funding gap for R&D of new vaccines with potential for global AMR impact.	**4a.** Funders, industry, governments, nongovernmental and supranational organizations, academic institutions and researchers should increase investments in vaccine candidates with anticipated benefits for AMR.	
	4b. Funders, including governments and nongovernmental organizations, product development sponsors and industry, should create novel financing mechanisms for late-stage vaccine evaluation, introduction, evaluation of new vaccine effectiveness and impact, and to ensure sufficient manufacturing capacity to meet global needs for vaccines expected to reduce AMR.	
5 Develop regulatory and policy mechanisms to accelerate approval and use of new vaccines that can reduce AMR.	**5a.** Vaccine development sponsors and regulatory authorities should systematically assess the potential to prevent and control AMR and related data packages generated in clinical development to expand knowledge of investigational product risk-benefit balance.	
	5b. Regulators and policy-makers should develop means to accelerate access to vaccines of urgent medical need, including impacts on AMR, without jeopardizing the required confidence in safety and efficacy.	
	5c. WHO, through its Product Development for Vaccines Advisory Committee (PDVAC) and Strategic Advisory Group of Experts (SAGE) on Immunization, and other stakeholders who shape progress in vaccine R&D should include evaluation of AMR impacts in their product landscape analyses and guidance.	
	5d. Vaccine development sponsors and regulators should discuss clinical research requirements for regulatory labeling to include specifications about impact on AMR and antimicrobial use.	
	5e. Sponsors of post-licensure vaccine evaluations, such as health-economic impact studies, should discuss with regulators and policy-makers, during the approval process, when and how to include evaluation of a vaccine's potential to reduce antimicrobial use and AMR in these studies.	

GOAL

Expand and share knowledge of vaccine impact on AMR

OBJECTIVES	ACTIONS	AUDIENCE
6 Improve methodologies and increase collection and analysis of relevant data to assess vaccine impact on AMR, including antimicrobial use.	**6a.** Normative bodies should provide guidance for health technology assessment and evaluation of vaccine impact on AMR and antimicrobial use.	
	6b. Funders and researchers should analyse existing datasets from epidemiologic studies, trials and routine surveillance in order to estimate vaccine impact on AMR.	
	6c. When relevant, sponsors, funders and investigators conducting new trials and studies using existing and candidate vaccines should assess vaccine impact on AMR, including antimicrobial use.	
	6d. Public health authorities at the global, national and subnational levels should enhance surveillance systems to link vaccination data with antimicrobial use and resistance data, with the greatest practical level of geographic and demographic granularity to enable interventions that focus on the most vulnerable. In resource-limited settings, building capacity for data collection and analysis should be included in immunization and AMR country action plans.	
	6e. Researchers should continue to generate new evidence on: ▪ how to use vaccines with the specific aim of controlling drug-resistant pathogens when highly prevalent or causing epidemics; ▪ how vaccines can complement other infection control strategies and stewardship efforts to prolong or restore effective use of antibiotics against specific pathogens; ▪ socioeconomic and ethical aspects of vaccine impact on AMR.	
	6f. Researchers and their sponsors should ensure that new data and evidence are made rapidly and publicly available through prompt public posting and scientific publications, preprints, and data-sharing platforms.	
7 Develop estimates of vaccine value to avert the full public health and socioeconomic burden of AMR.	**7a.** Funders should support researchers to develop and improve methodologies for estimating impact of vaccines on AMR.	
	7b. Health delivery payers and investors in R&D should develop and use standardized health technology assessments and value-attribution frameworks to inform the estimation of the full value of vaccines to prevent and control AMR.	

Vaccine	WHO recommendation	Global coverage in 2018[a]	WHO coverage target[b]	Vaccine impact on AMR
PCV	All children, through routine immunization.	47%	90% nationally, 80% at district level.	Reduces resistant and non-resistant pneumococcal disease; reduces antibiotic use in children.[c]
TCV	In endemic countries, programmatic delivery to children 9 months old or in the second year of life and catch-up campaign in children up to 15 years of age.	NA	Access to be prioritized in settings with high endemicity and high levels of AMR.	Modelling suggests vaccine use will proportionally reduce incidence of resistant and non-resistant typhoid, including number of chronic typhoid carriers.[d]
Hib vaccine	All children, through routine immunization.	72%	90% nationally, 80% at district level.	Reduces resistant and non-resistant Hib disease; may have reduced overall proportion of resistant strains. Some evidence that Hib introduction modestly reduced antibiotic prescriptions among children <5 years.[c]
Influenza vaccines	All pregnant women, children 6-59 months, adults >65 years, people with chronic medical conditions and health-care workers.	NA	Varies according to risk group.	Good evidence that influenza vaccine reduces antibiotic use by reducing misuse of antibiotics and treatment of secondary bacterial infections.[e]
Rotavirus vaccine	All children, through routine immunization.	35%	90% nationally, 80% at district level.	Expected to reduce antibiotic use but no confirmatory data available.
Measles vaccine	All children, through routine immunization.	69%	90% nationally, 80% at district level	Expected to reduce antibiotic use against secondary bacterial complica-tions, but no confirmatory data available.

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