5th WAidid CONGRESS

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Impact of vaccines on antimicrobial resistance

Sepulcri Chiara, ID specialist, PhDc
University of Genova, Department of Health Sciences (DISSAL)

WAidid
World Association for Infectious Diseases and Immunological Disorders

Disclosures

- None

Antimicrobial resistance (AMR): a global health threat

4.71 millions

deaths associated with bacterial AMR in 2021

Since 1990:

+50% deaths in children under 5 years

+80% in adults over 70 years

+56%

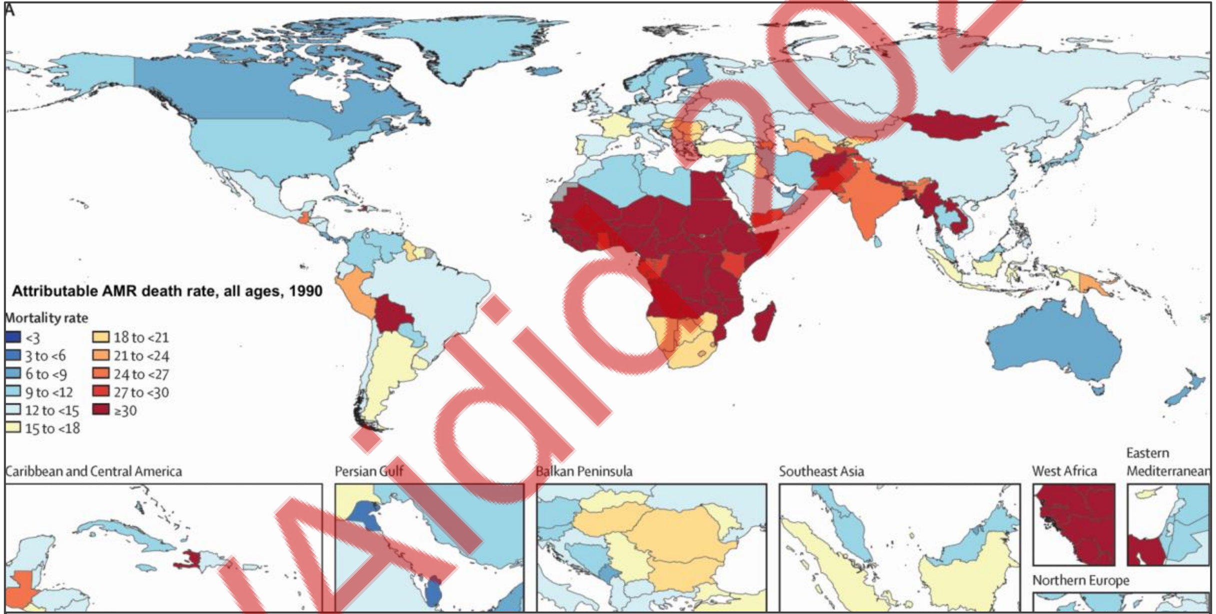
resistance in key pathogens:
Acinetobacter spp. and *Klebsiella spp.*

+46%

antibiotic consumption between 2000 and 2018

Browne AJ, et al. Lancet Planet Health. 2021;5(12):e893-e904.
World Health Organization. Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report: 2022
Naghavi, M et al. The Lancet, Volume 404, Issue 10459, 1199 - 1226

Antimicrobial resistance (AMR): a global health threat



Adapted from Naghavi et al. The Lancet, Volume 404, Issue 10459, 1199 - 1226

Forecast: 8.22 million (6·85–9·65) deaths associated with AMR in 2050. Highest all-age AMR mortality rate: south Asia and Latin America and the Caribbean

Naghavi, M et al. The Lancet, Volume 404, Issue 10459, 1199 - 1226

Antimicrobial resistance (AMR): contributing factors

Over-prescribing of antibiotics[1]

Patients not taking antibiotics as prescribed[2]

Unnecessary antibiotics used in agriculture[1]

Poor infection control in hospitals and clinics[2]

Poor hygiene and sanitation practices[2]

Lack of rapid laboratory tests[2,3]

COVID-19 healthcare disruption and antimicrobial overuse likely promoted AMR[4]

AMR, antimicrobial resistance.

1. Tang KWK, et al. Br J Biomed Sci. 2023;80:11387.
2. World Health Organization. Antibiotic Resistance Fact Sheet. 2023. https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance.
3. O'Neill J. Rapid diagnostics: Stopping unnecessary use of antibiotics. The review on antimicrobial resistance. 2015.
4. Segala FV, et al. *Viruses*. 2021;13(11):2110.

Antimicrobial resistance (AMR): tools to fight it

- Stewardship programs
- Reduce resistant reservoirs
- Improved diagnostics
- Education
- New drugs and VACCINES
- Infection control

Adapted from Fishman N. *Am J Infect Control.* 2006;34:S55-S64.

Antimicrobial resistance (AMR): priority pathogens

Critical group

- Enterobacterales — carbapenem-resistant
- Enterobacterales — third-generation cephalosporin-resistant
- *Acinetobacter baumannii* — carbapenem-resistant
- *Mycobacterium tuberculosis*, rifampicin-resistant[a]

[a]RR-TB was included after an independent analysis with parallel criteria and subsequent application of an adapted MCDA matrix.

High group

- *Salmonella* Typhi — fluoroquinolone-resistant
- *Shigella* spp. — fluoroquinolone-resistant
- *Enterococcus faecium* — vancomycin-resistant
- *Pseudomonas aeruginosa* — carbapenem-resistant
- Non-typhoidal *Salmonella* — fluoroquinolone-resistant
- *Neisseria gonorrhoeae* — third-generation cephalosporin,and/or fluoroquinolone-resistant
- *Staphylococcus aureus* — methicillin-resistant

Medium group

- Group A Streptococci — macrolide-resistant
- *Streptococcus pneumoniae* — macrolide-resistant
- *Haemophilus influenzae* — ampicillin-resistant
- Group B Streptococci — penicillin-resistant

Antimicrobial resistance (AMR): how can vaccines help?

1. Direct effect on pathogens transmission and associated antibiotic use in vaccinated populations + herd effect in unvaccinated populations

2. Prevent inappropriate antibiotic prescriptions for viral illnesses

3. Reduce hospitalizations and antibiotic prescription for secondary bacterial infections/hospital acquired infections

Adapted from Kim C et al., BMJ Glob Health 2023;8:e01134

1 Direct effect on pathogens transmission and associated antibiotic use in vaccinated populations: PNEUMOCOCCUS

Pneumococcus: resistance mechanisms and epidemiology

Multiple mechanisms of resistance:

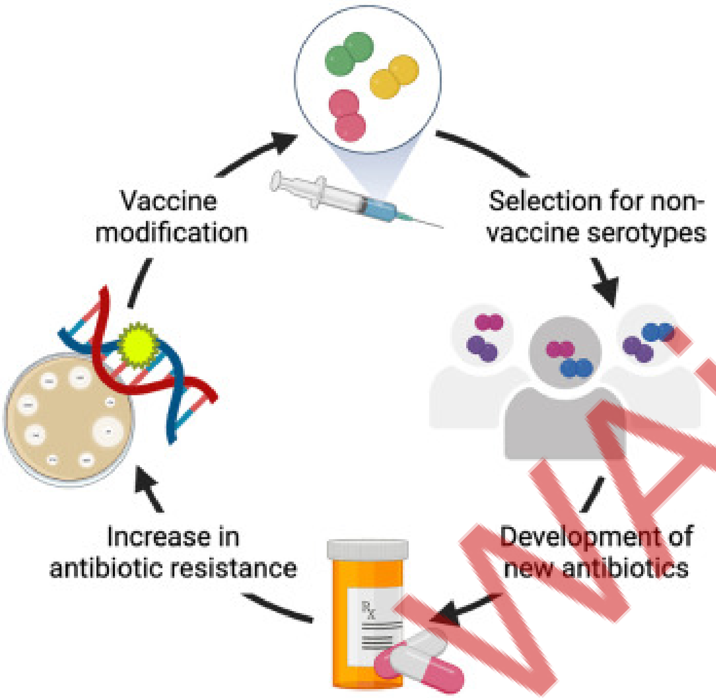
- **Beta-lactams**: structural changes in PBPs
- **Macrolides**: target site modification
- **Fluoroquinolones**: point mutations in topoisomerase/gyrase
- **Combined macrolide/beta-lactam resistance**

Fig. 19 *Streptococcus pneumoniae*. Percentage of penicillin[a] non-wild-type[b] invasive isolates, by country, EU/EEA, 2021

9% combined macrolide+penicillin resistance

ECDC Antimicrobial resistance surveillance in Europe 2023 - 2021 data.

1 Direct effect on pathogens transmission and associated antibiotic use in vaccinated populations: PNEUMOCOCCUS



Pneumococcus: model pathogen of vaccine-antibiotic resistance interplay

Strategies deployed by pneumococcus under vaccines/antibiotics selective pressure include:

- serotype replacement
- serotype switch
- acquired resistance from non-pneumococcal streptococci in shared ecological niches

Johnson CN, Cell Chemical Biology 31, February 15, 2024

1 Direct effect on pathogens transmission and associated antibiotic use in vaccinated populations: PNEUMOCOCCUS

2000
PCV7 in children

2012-13
PCV13 in children
Adults at risk

2014-19
PCV13 in ≥65

2021
PCV15/20 in adults

2022-23
PCV15/20 in children

USA

Decrease in rate of non-susceptible invasive pneumococcal disease in all age groups (43.9 to 3.2 among children <5 years and from 19.8 to 9.4 in adults)

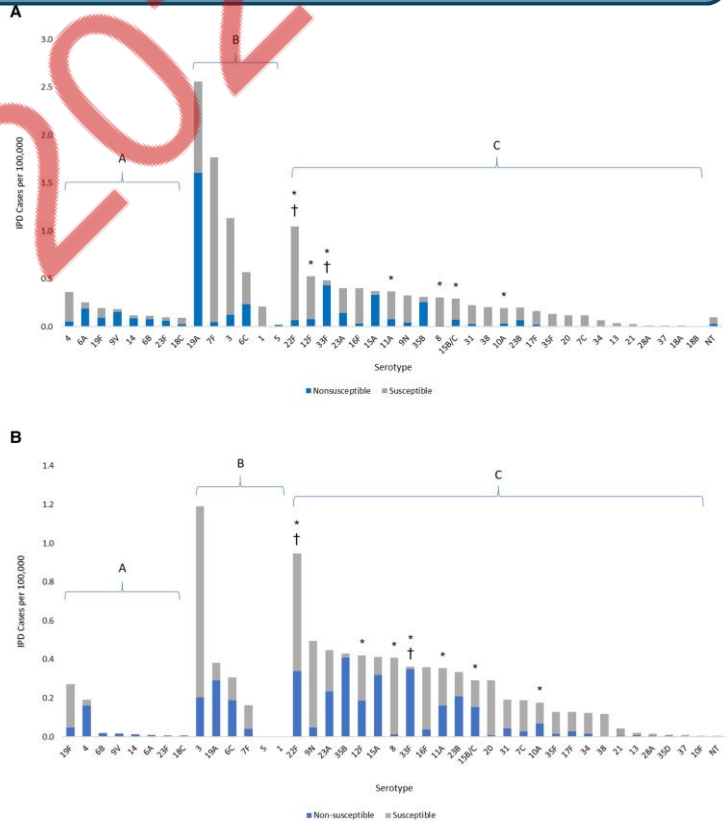
SEROTYPE REPLACEMENT

Increase in non-vaccine type infections in all age groups, especially in ≥65 years (2.3 to 7.2)
19A after PCV7, 35B, 33F, 22F, and 15A after PCV13

Expected increase coverage on non-vaccine serotypes infections +19% and +34%

SEROTYPE REPLACEMENT?

Serotype 35B not covered, associated to high-level resistance



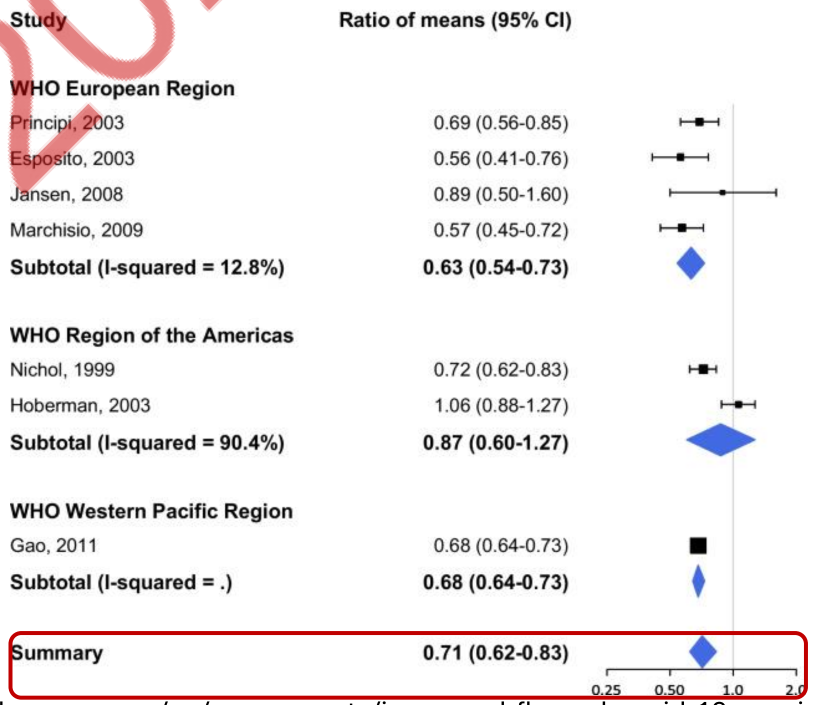
J Infect Dis, Volume 226, Issue 2, 15 July 2022, Pages 342–351

2 Prevent inappropriate antibiotic prescriptions for viral illnesses

Respiratory illnesses: Influenza

- **Up to 84% of patients with viral respiratory illnesses are inappropriately prescribed antibiotics**
- For the 2023-2024 influenza season, ECDC reports coverage ranging from 12% to 78% in adults ≥65, with only two countries exceeding 75%

Meta-analysis of studies assessing effect of influenza vaccine on individual antibiotic prescriptions and antibiotic consumption in the community, 17 RCTs included



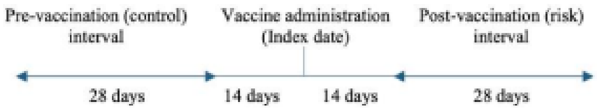
https://www.ecdc.europa.eu/en/news-events/increased-flu-and-covid-19-vaccina coverage-recommended-risk-groups-eueea-ahead

Antimicrob Resist Infect Control. 2023 Jul 14;12:70

2 Prevent inappropriate antibiotic prescriptions for viral illnesses

Respiratory illnesses: SARS-CoV-2

ONTARIO, CANADA: Self-Controlled Risk-Interval Study on adults ≥ 65 years at their first, second, and/or third COVID-19 vaccine dose



469 923 vaccine doses include

Higher effect during periods with high SARS-CoV-2 positivity

Antibiotic Group	Post-Vaccination (Risk) Interval[a]	Pre-Vaccination (Control) Interval[a]	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[b]	Adjusted Risk Difference Per 10 000 Vaccine Doses (95% CI)[b]
All antibiotics					
All doses	230 276/469 923 (49.0%)	239 647/469 923 (51.0%)	.961 (.956–.966)	.973 (.968–.978)	9 (7–11)
Dose 1	77 149/156 177 (49.4%)	79 028/156 177 (50.6%)	.976 (.967–.986)	.983 (.973–.993)	6 (2–9)
Dose 2	79 971/157 092 (50.9%)	77 121/157 092 (49.1%)	1.037 (1.027–1.047)	1.010 (.994–1.026)	−3 (−8–2)
Dose 3	73 156/156 654 (46.7%)	83 498/156 654 (53.3%)	.876 (.867–.885)	.909 (.897–.921)	34 (30–39)
Respiratory antibiotics[c]					
All doses	125 758/257 812 (48.8%)	132 054/257 812 (51.2%)	.952 (.945–.959)	.961 (.953–.968)	7 (6–9)
Dose 1	41 802/84 122 (49.7%)	42 320/84 122 (50.3%)	.988 (.974–1.001)	.993 (.980–1.007)	1 (−1–4)
Dose 2	41 617/83 081 (50.1%)	41 464/83 081 (49.9%)	1.004 (.990–1.017)	.997 (.983–1.013)	1 (−2–3)
Dose 3	42 339/90 609 (46.7%)	48 270/90 609 (53.3%)	.877 (.866–.889)	.898 (.885–.911)	22 (20–25)
Urinary antibiotics[d]					
All doses	79 707/160 431 (49.7%)	80 724/160 431 (50.3%)	.987 (.978–.997)	.996 (.987–1.006)	0 (−1–2)
Dose 1	26 491/53 337 (49.7%)	26 846/53 337 (50.3%)	.987 (.970–1.004)	.989 (.973–1.006)	1 (−1–3)
Dose 2	28 522/54 678 (52.2%)	26 156/54 678 (47.8%)	1.090 (1.072–1.109)	1.029 (.998–1.061)	−3 (−7–0)
Dose 3	24 694/52 416 (47.1%)	27 722/52 416 (52.9%)	.891 (.876–.906)	.958 (.934–.983)	5 (2–8)

Jorgensen et al . CID 2024:79 (15 August 2024)

2 Prevent inappropriate antibiotic prescriptions for viral illnesses

Respiratory illnesses: RSV?

General practice antibiotic prescriptions attributable to Respiratory Syncytial Virus by age and antibiotic class: An ecological analysis of the English population

Lucy Miller, Thomas Beaney, Russel Hope, Mark Cunningham, Julie V. Robotham, Koen B. Pouwels, Cèire E. Costelloe

doi: https://doi.org/10.1101/2024.10.31.24316265

This article is a preprint and has not been peer-reviewed [what does this mean?]. It reports new medical research that has yet to be evaluated and so should *not* be used to guide clinical practice.

UK Study with surveillance data from 2015-2018 associations between weekly counts of general practice antibiotic prescriptions and laboratory-confirmed respiratory infections

2.1% antibiotic prescription attributable to RSV (640,00(prescriptions/year), mostly in adults ≥ 65 years
Infants 6-23 months had the highest average annual rate at 6,580 prescriptions per 100,000 individuals

Respiratory syncytial virus (RSV_2)

A vaccine against severe RSV infection given to 70% of infants, with 2-year efficacy of 70% [RSV_2]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Respiratory syncytial virus	Infants	2 years	Efficacy: 70% Coverage: 70%	*Not assessed*
Vaccine name: RSV_2				Feasibility of vaccine development and implementation: LOW

	WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
Antibiotic use	AFR	11 (3.7–22) million	5.4 (1.8–11) million
	EUR	4.2 (1.5–9.5) million	2.0 million (710 000–4.6 million)
	EMR	5.2 (1.4–13) million	2.6 million (710 000–6.4 million)
	SEAR	3.2 million (800 000–6.8 million)	1.5 million (390 000–3.3 million)
	AMR	3.0 million (750 000–6.7 million)	1.5 million (370 000–3.3 million)
	WPR	2.3 million (630 000–4.6 million)	1.1 million (310 000–2.3 million)
	GLOBAL	29 (9.8–62) million	14 (4.8–30.0) million

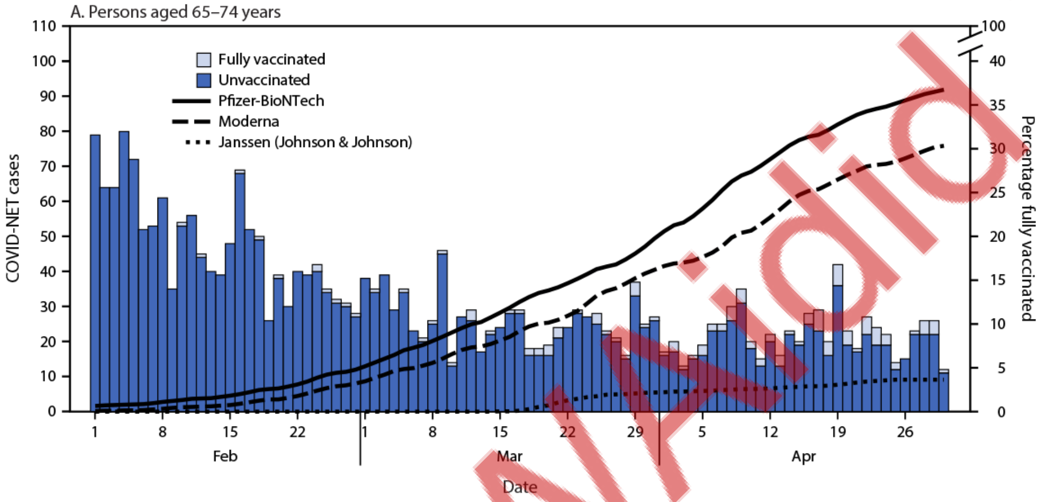
AMR: antimicrobial resistance; DDD: defined daily doses; UI: uncertainty interval; WHO: World Health Organization.

Regions: AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region.

Estimating the impact of vaccines in reducing antimicrobial resistance and antibiotic technical report. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3 IGO

3 Reduce hospitalizations and antibiotic prescription for secondary bacterial infections/hospital acquired infections

COVID-19 hospitalization rates by vaccine status overtime



Unlike influenza, prevalence of bacterial co/super-infections in COVID-19 in low (4–6%)

Despite this, up to 60% of patients hospitalized for COVID-19 receive antibiotics

Bassetti et al.; Expert Opin Pharmacother. 2023;24(15):1679-1684.
https://www.cdc.gov/mmwr/volumes/70/wr/mm7032e3.htm *Weekly* / August 13, 2021 / 70(32);1088-

Vaccines as a tool for AMR reduction

- Increase vaccine coverage and improve vaccines already in use
- Invest on research on new vaccines

Estimating the impact of vaccines in reducing antimicrobial resistance and antibiotic use

World Health Organization

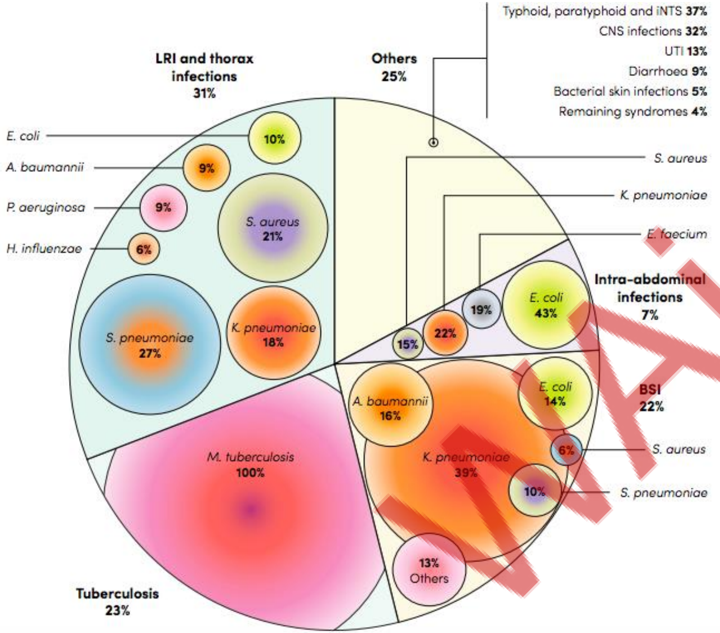
10 October 2024
Technical document

The report finds that existing vaccines could prevent up to 106,000 AMR-associated deaths per year, as well as 9.1 million disability-adjusted life years (DALYs), USD 861 million in hospital costs, and USD 5.9 billion in productivity losses. They could also reduce annual antibiotic use by 142 million defined daily dosages.

Estimating the impact of vaccines in reducing antimicrobial resistance and antibiotic use: technical report. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO

Vaccines as a tool for AMR reduction

Estimated potential vaccine-preventable deaths associated with AMR by infectious syndrome and pathogen in 2019

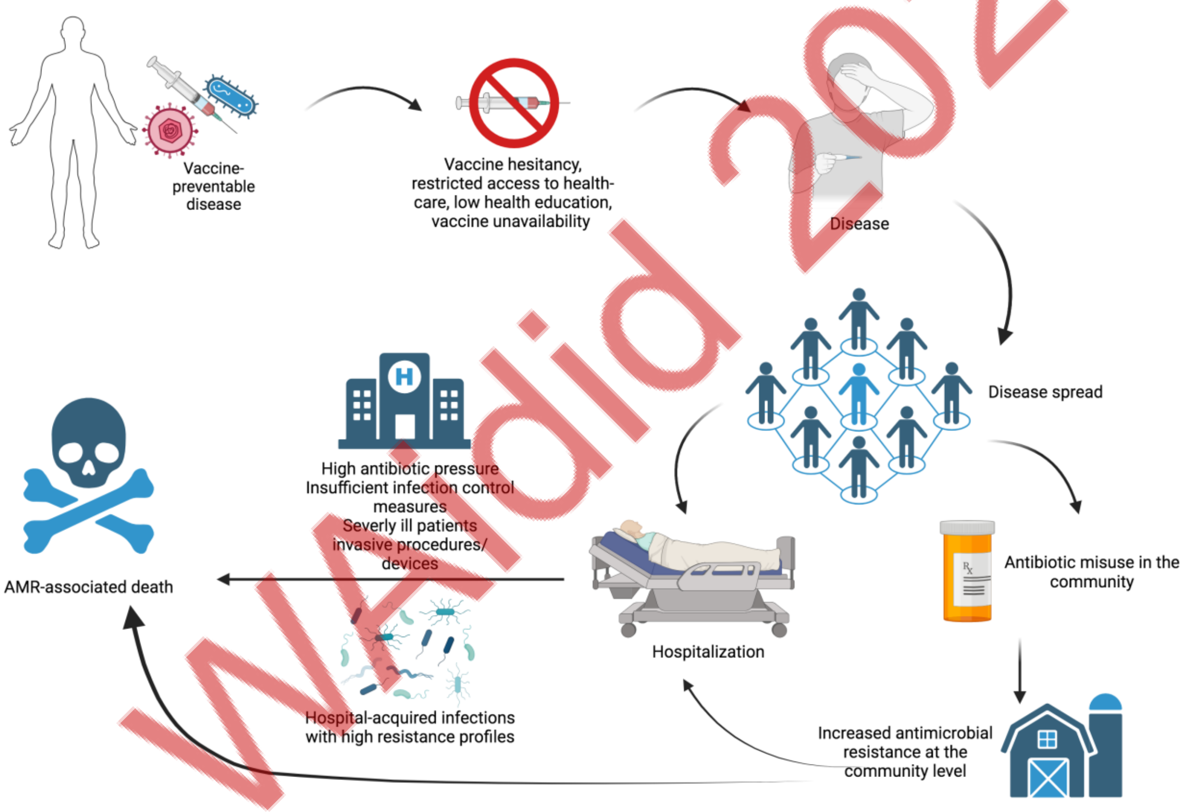


Recommendations

- Include impact on AMR in vaccine cost-effectiveness studies
- Accelerate introduction of typhoid vaccines in high-burden countries
- Increase coverage of influenza, rotavirus, pneumococcus vaccine
- Reduce price of malaria vaccine to facilitate introduction
- Enable and accelerate broad and rapid deployment of novel TB vaccines
- Inclusion of AMR endpoints in clinical trials

Estimating the impact of vaccines in reducing antimicrobial resistance and antibiotic use: technical report. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO

Break The Chain!



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Thank you for your attention