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# Antimicrobial Therapy: Now and the Future

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# Disclosures

## ▶ **Consulting**

- ▶ Gilead
- ▶ GSK
- ▶ Moderna
- ▶ Shionogi
- ▶ Meiji Seika
- ▶ bioMerieux
- ▶ Pfizer
- ▶ AbbVie

## ▶ **Speaking fees**

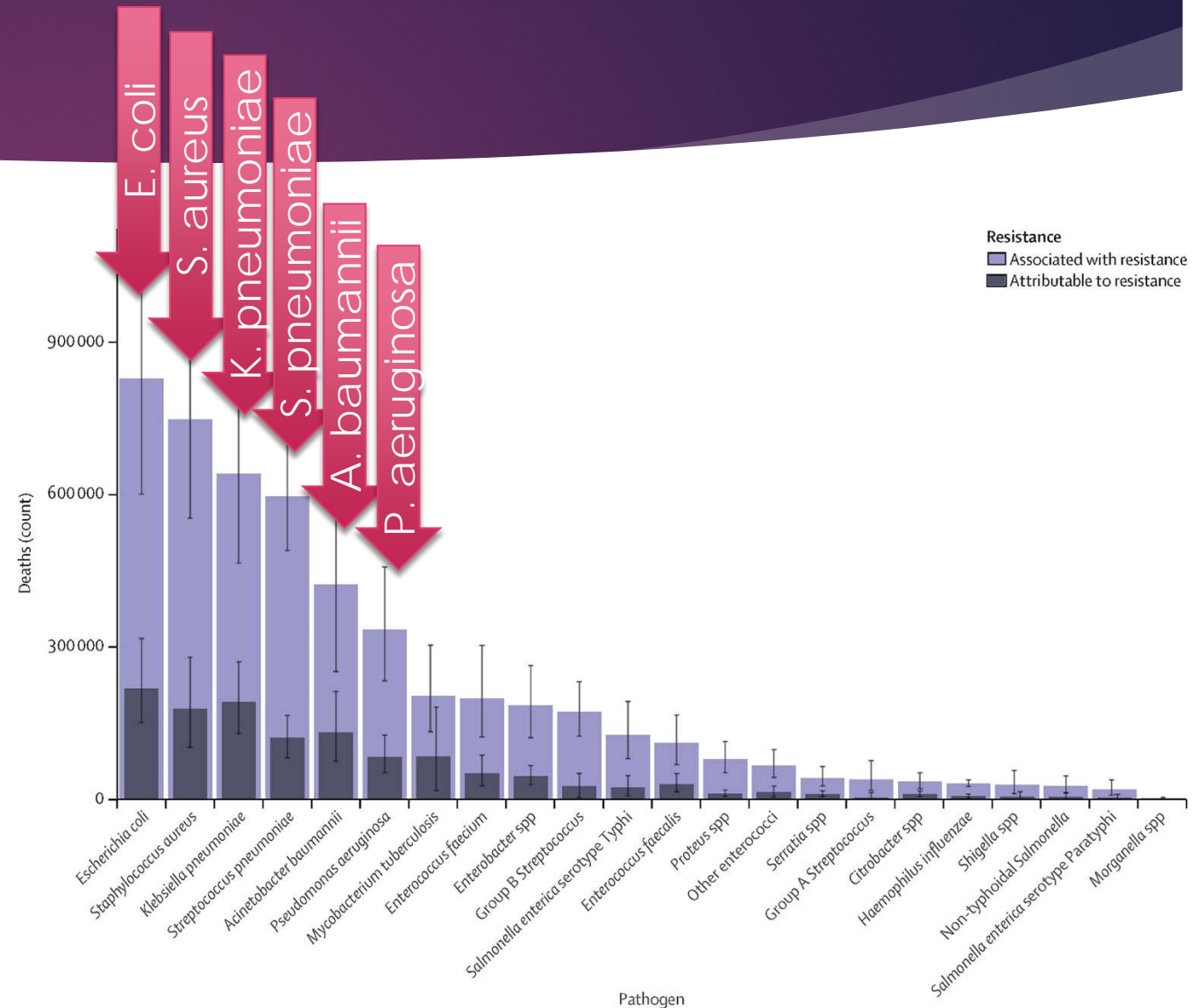
- ▶ MSD
- ▶ Shionogi

## ▶ **Research grants**

- ▶ National Institutes of Health
- ▶ Japan Agency for Medical Research and Development
- ▶ Japan Society for the Promotion of Science
- ▶ Shionogi
- ▶ Entasis

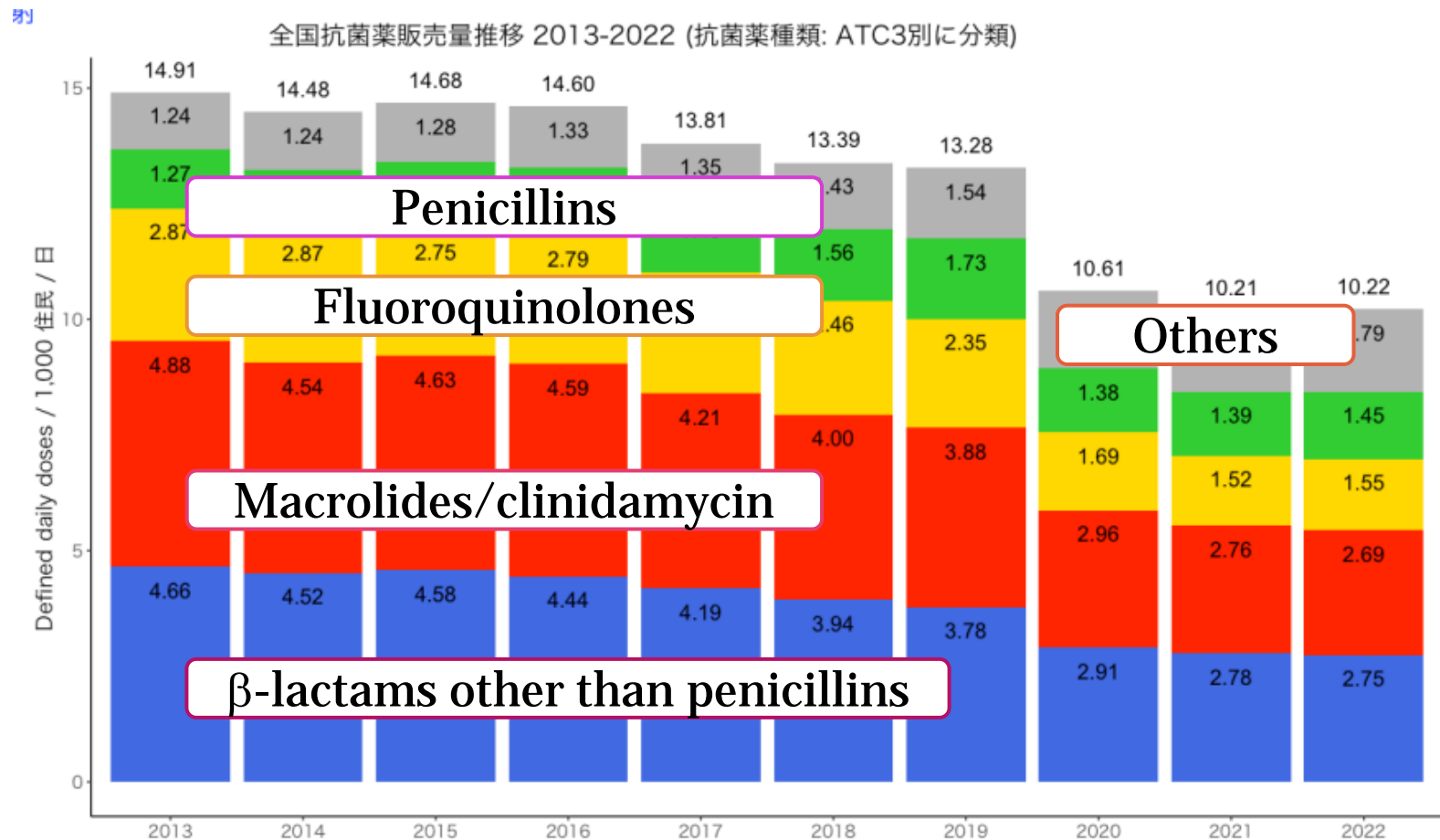
# Antimicrobial resistance as a global threat

- ▶ 4.95 million people worldwide died in 2019 *with* AMR bacterial infections
- ▶ 1.27 million people die *from* AMR bacterial infections



# Antimicrobial sales/use in Japan

- ▶ Antimicrobial use has declined significantly in Japan over the last decade primarily due to:
  - ▶ implementation of the AMR Action Plan
  - ▶ COVID-19 pandemic





# Antimicrobial equity and stewardship

- ▶ Antimicrobials face unique challenges:
  - ▶ Need to expand access
  - ▶ Need to ensure appropriate use/prevent inappropriate access

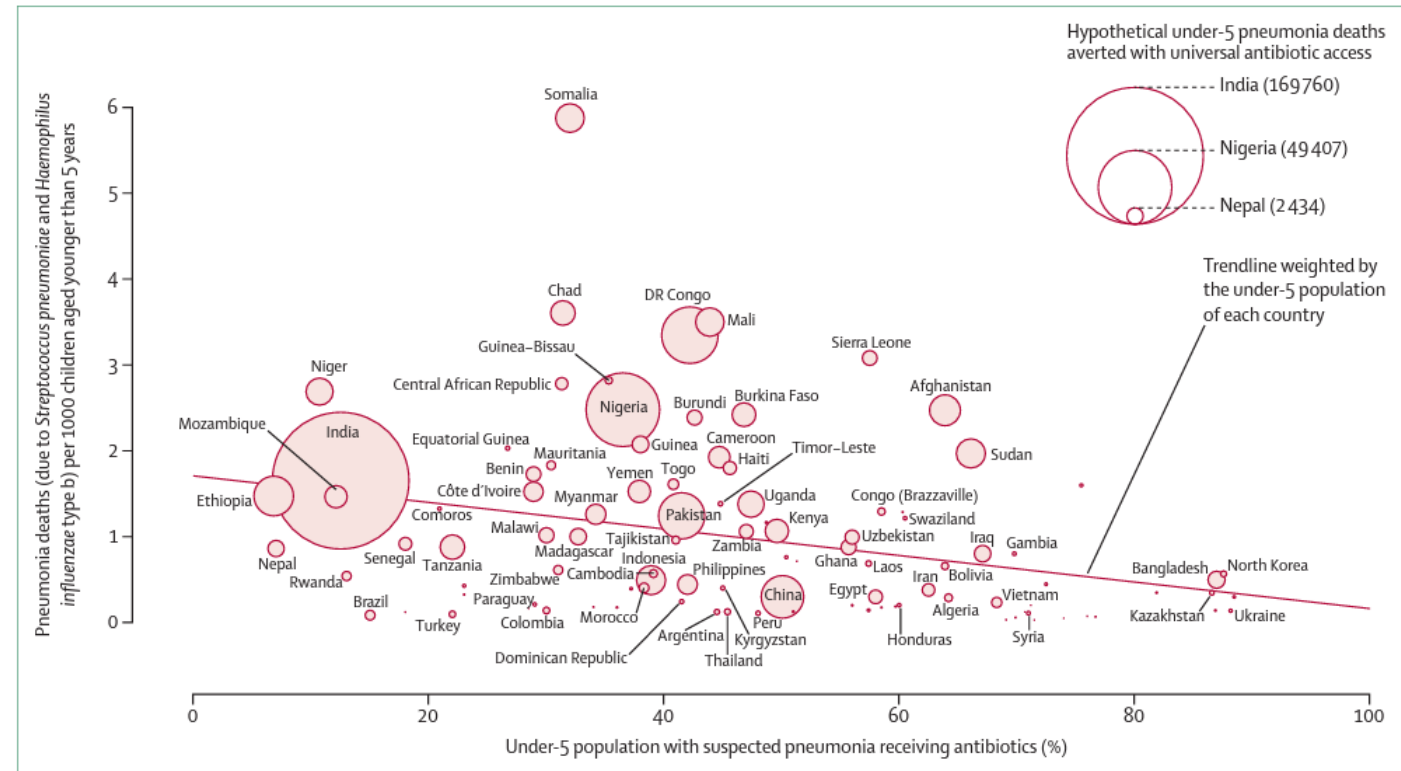
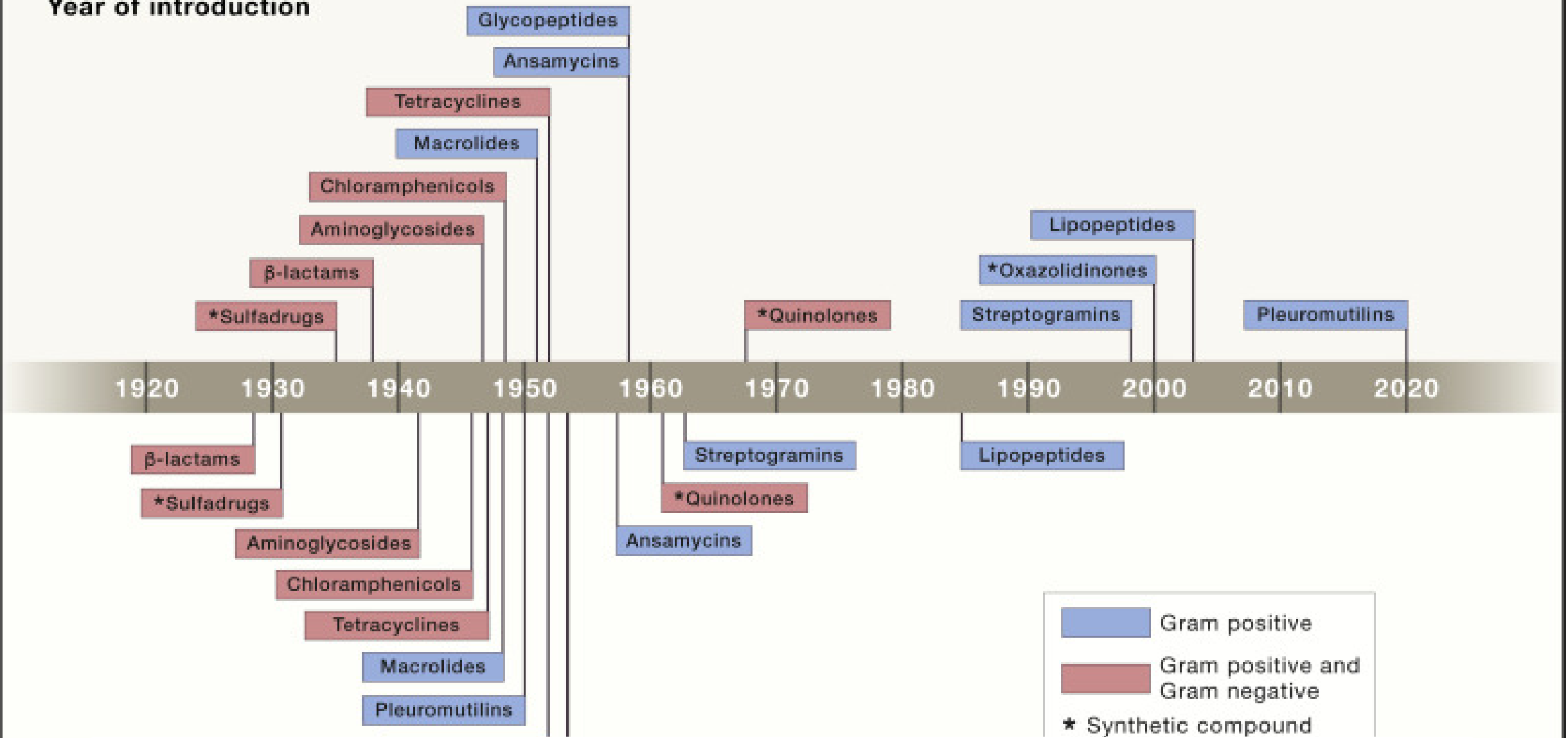


Figure 1: Estimated pneumonia deaths avertable in under-5 populations with improved antibiotic access

Countries with less than 100 deaths averted are not labelled. Data on under-5 population with suspected pneumonia receiving antibiotics are from 1990 to 2013; data from the most recent year reported is used, when available.

Year of introduction



Few new classes of antibiotics have been introduced in 50 years

Year of discovery

# Develop antimicrobials is difficult

- ▶ Limited targets
- ▶ Development of resistance
- ▶ Change in epidemiology
- ▶ Only used for short periods
- ▶ Expensive, difficult trials
- ▶ Inadequate return on investment

# Changing landscape

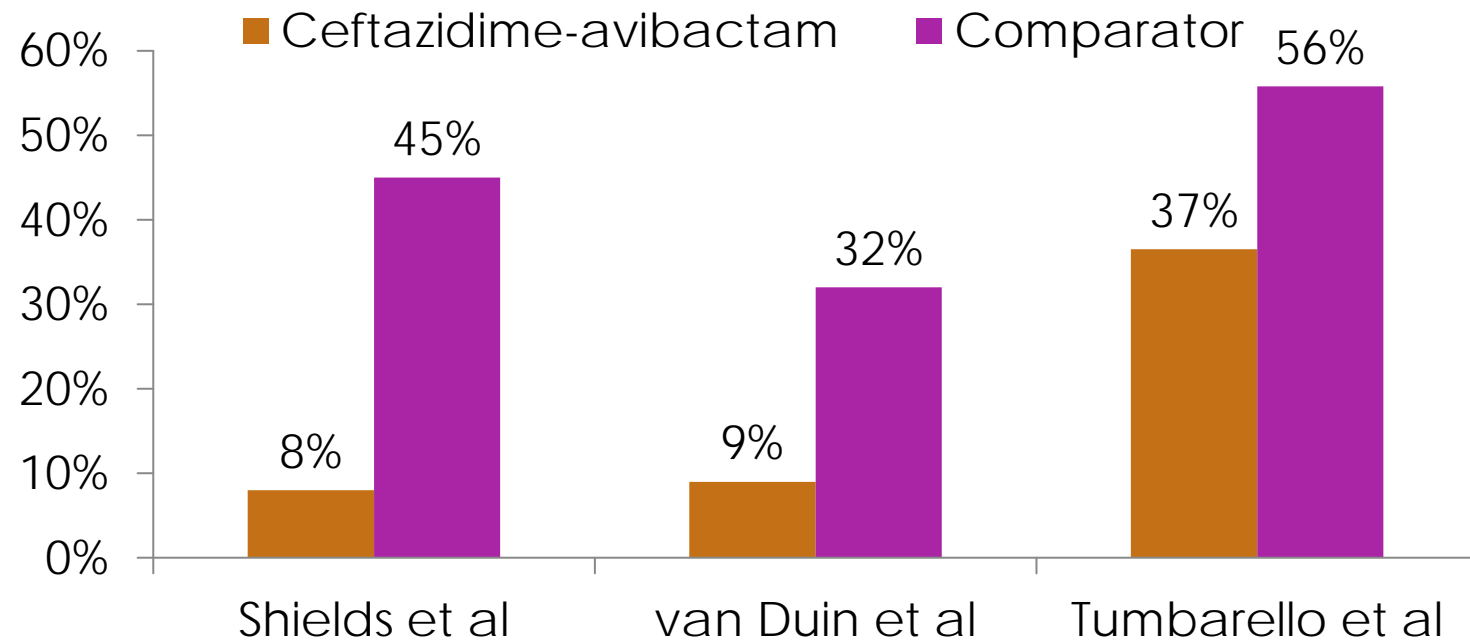
- ▶ A number of new agents have been approved since 2014, especially those targeting carbapenem-resistant pathogens
  - ▶ Ceftazidime-avibactam      Approved globally
  - ▶ Meropenem-vaborbactam      Approved in US and EU
  - ▶ Plazomicin      Approved in US
  - ▶ Eravacycline      Approved in US and EU
  - ▶ Imipenem-cilastatin-relebactam      Approved in US, EU
  - ▶ Cefiderocol      Approved in US and EU



# New agents save lives

- ▶ Ceftazidime-avibactam is clearly superior to colistin in infections caused by carbapenem-resistant *Enterobacterales*, especially KPC-producing ones

## 30-day all-cause mortality



Shields RK, et al. Antimicrob Agents Chemother 2017;61:e00883-17

van Duin D, et al. Clin Infect Dis 2018;66:163

Tumbarello M, et al. Clin Infect Dis 2019;68:355

# New agents are expensive

- ▶ Ceftazidime-avibactam US\$11,630 (10 days)
- ▶ Meropenem-vaborbactam US\$13,120 (10 days)
- ▶ Eravacycline US\$2,160 (10 days)
- ▶ Imipenem-cilastatin-relebactam US\$12,560 (10 days)
- ▶ Cefiderocol US\$13,270 (10 days)

# New agents may not sustain themselves commercially

- ▶ Plazomicin – new aminoglycoside with robust activity against carbapenem-resistant *Enterobacteriaceae*
- ▶ Eravacycline – new tetracycline with activity against carbapenem-resistant *Enterobacteriaceae* and *Acinetobacter*

ACHAOGEN

## Achaogen, Inc. Announces Results of Auction for Substantially All Company Assets

June 06, 2019 18:46 ET | Source: [Achaogen, Inc.](#)

SOUTH SAN FRANCISCO, Calif., June 06, 2019 (GLOBE NEWSWIRE) -- Achaogen, Inc., a biopharmaceutical company developing and commercializing innovative antibacterial agents to address multi-drug resistant (MDR) gram-negative infections, announced today it has

La Jolla PHARMACEUTICAL TETRAPHASE PHARMACEUTICALS

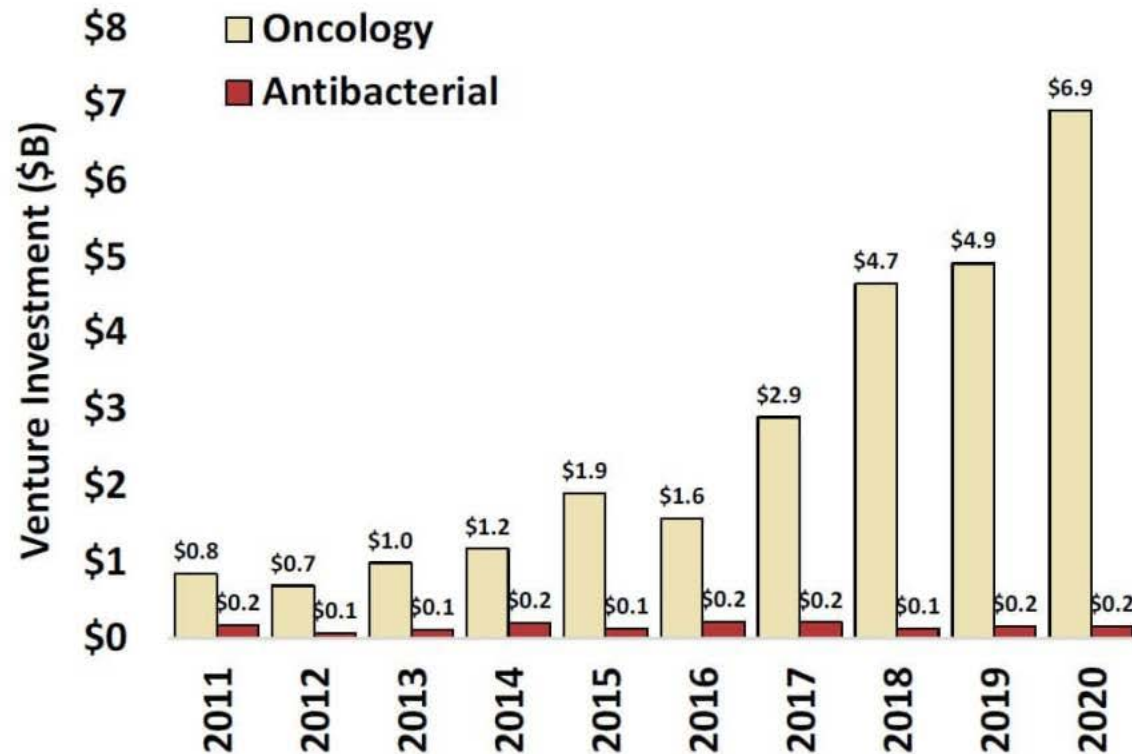
## La Jolla Pharmaceutical Company Announces the Closing of Acquisition of Tetrphase Pharmaceuticals, Inc.

-Combined Company Offers Two Innovative Therapies to Treat Patients Suffering from Life-threatening Diseases-

July 28, 2020 16:15 ET | Source: [La Jolla Pharmaceutical Company](#); [Tetrphase Pharmaceuticals, Inc.](#)

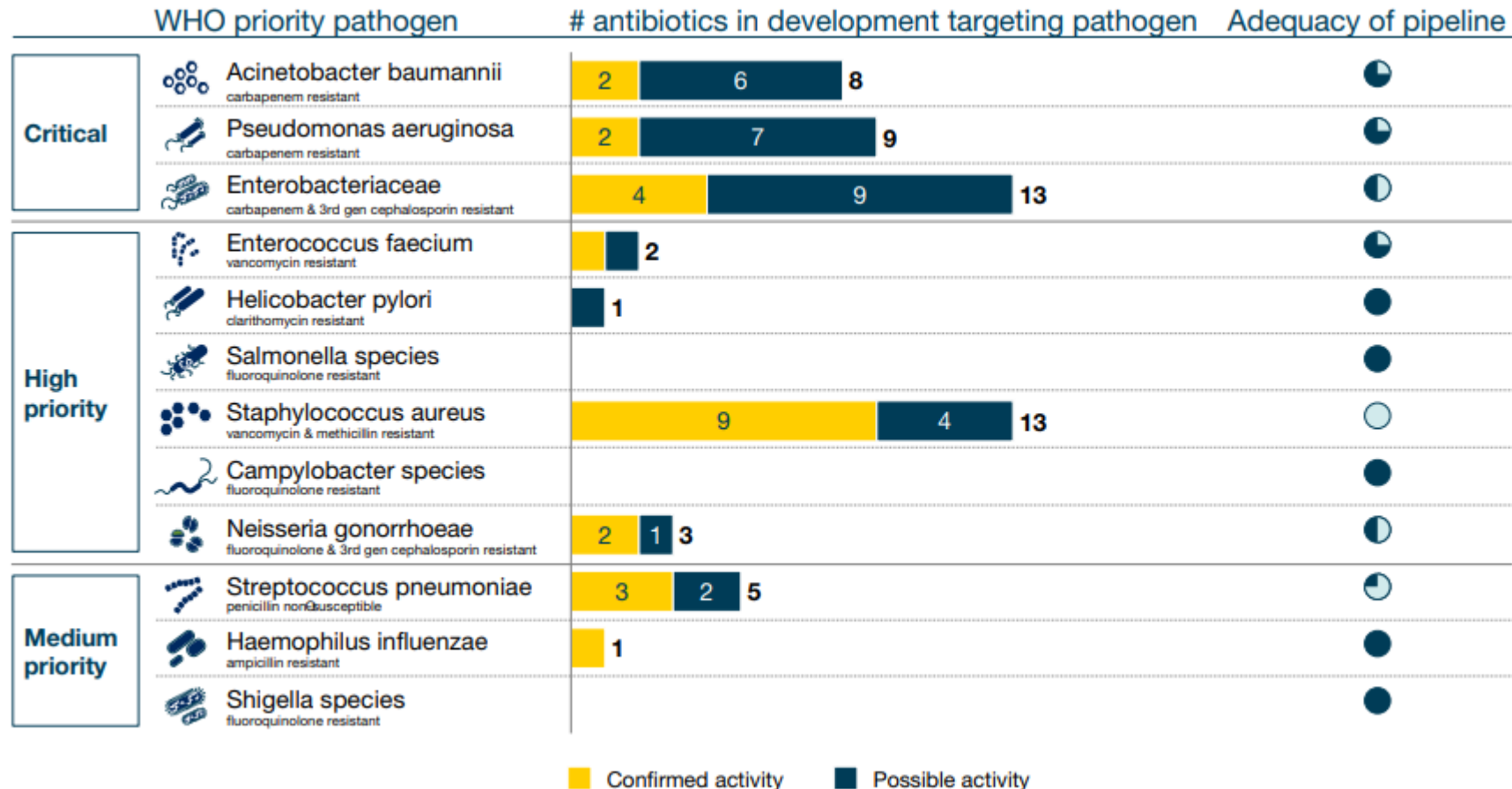
# The market does not support antimicrobials

2011-2020 VENTURE INVESTMENT INTO U.S. COMPANIES WITH LEAD NOVEL DRUG PROGRAMS IN ONCOLOGY VS. ANTIBACTERIALS





# The pipeline is insufficient to meet the AMR threat

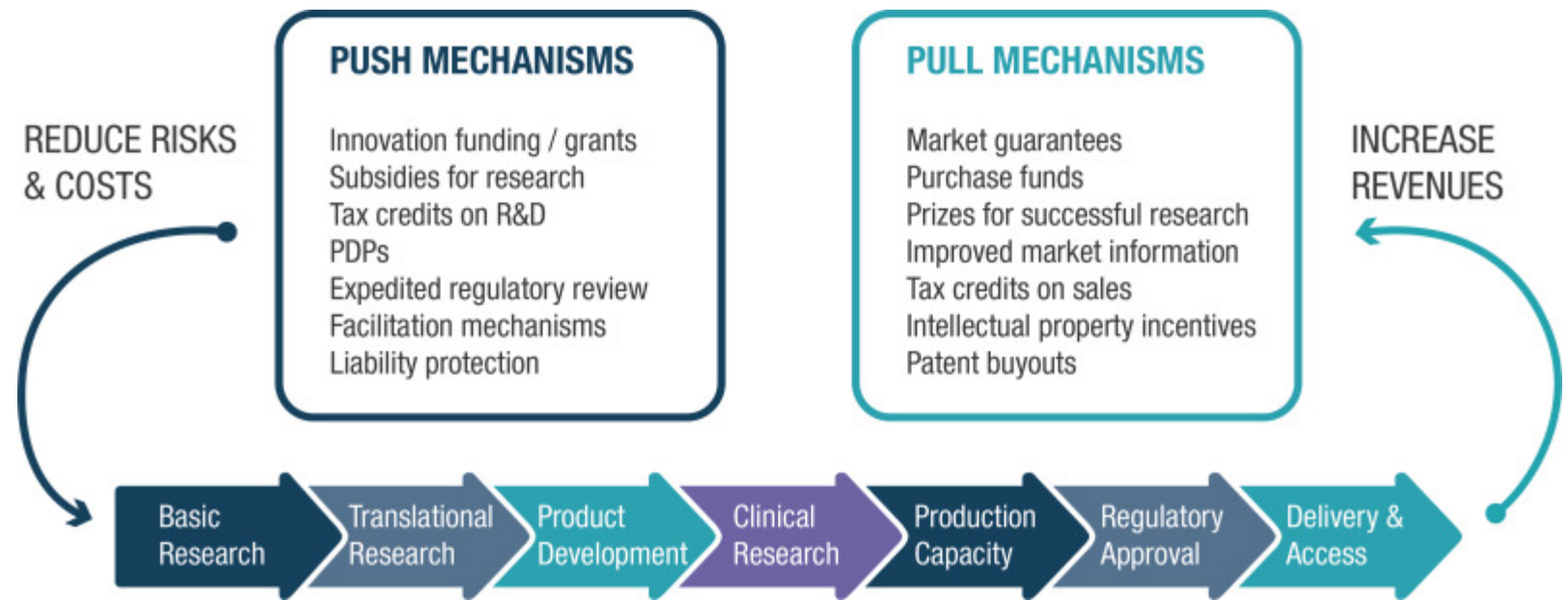


- There is disproportionate development activity targeting pathogens such as *s. aureus*, whereas there is no development activity for other pathogens such as shigella
- Expert input suggests only 1-3 priority pathogen (*s. aureus*) have somewhat sustainable pipelines



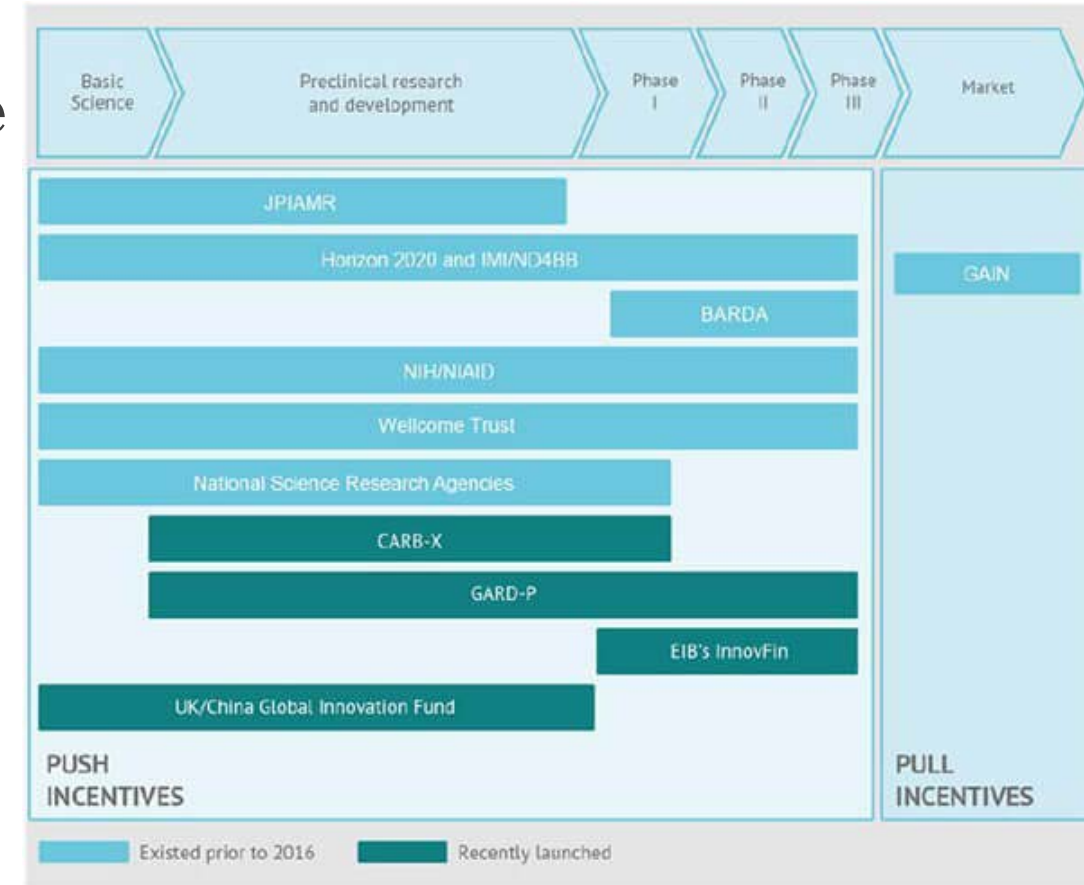
# The pipeline is insufficient to meet the AMR threat

- ▶ **Push incentive** -> supports innovation, research and development of new antimicrobials
- ▶ **Pull incentive** -> rewards new antimicrobials to ensure developers' viability



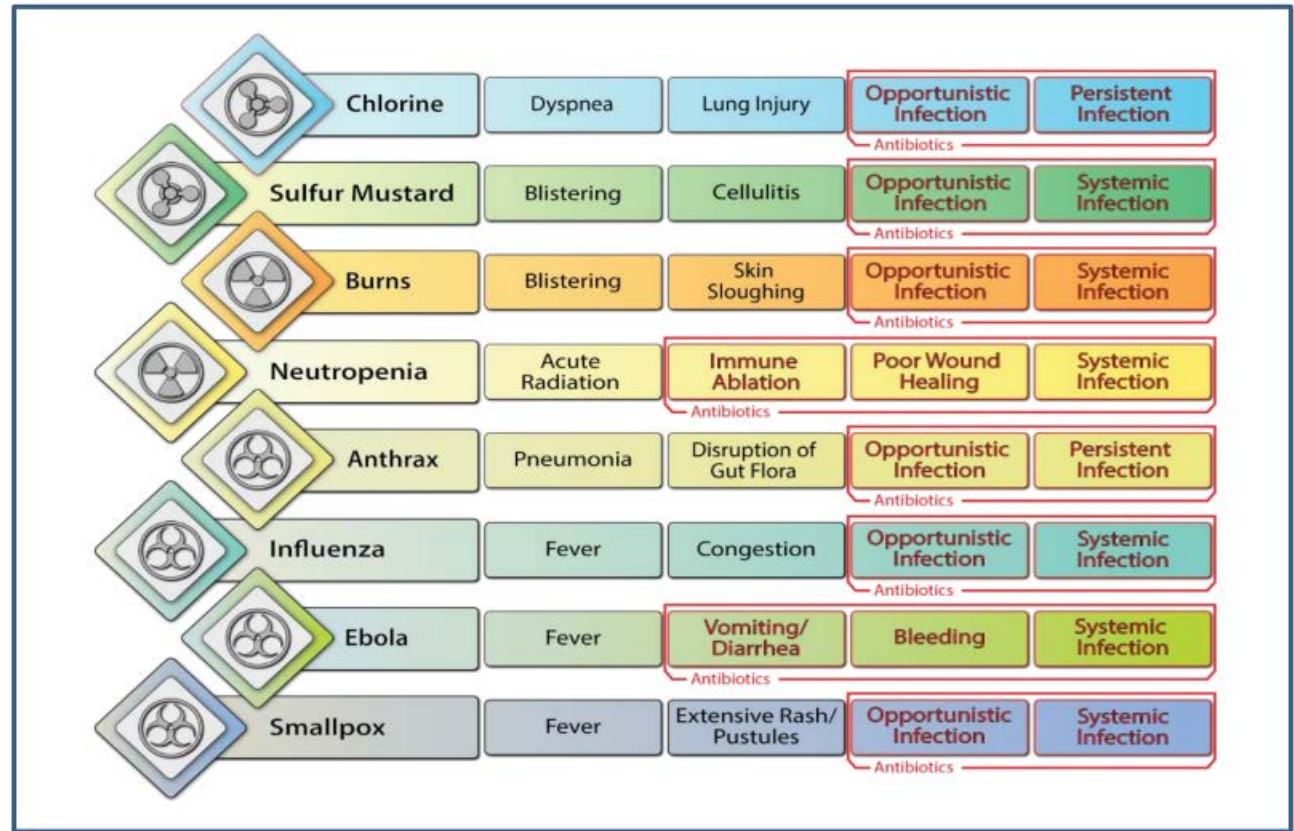
# Push incentives at work

- ▶ Push incentives (non-dilutive R&D support) fit the traditional model and have generally worked well



# Push incentive - BARDA

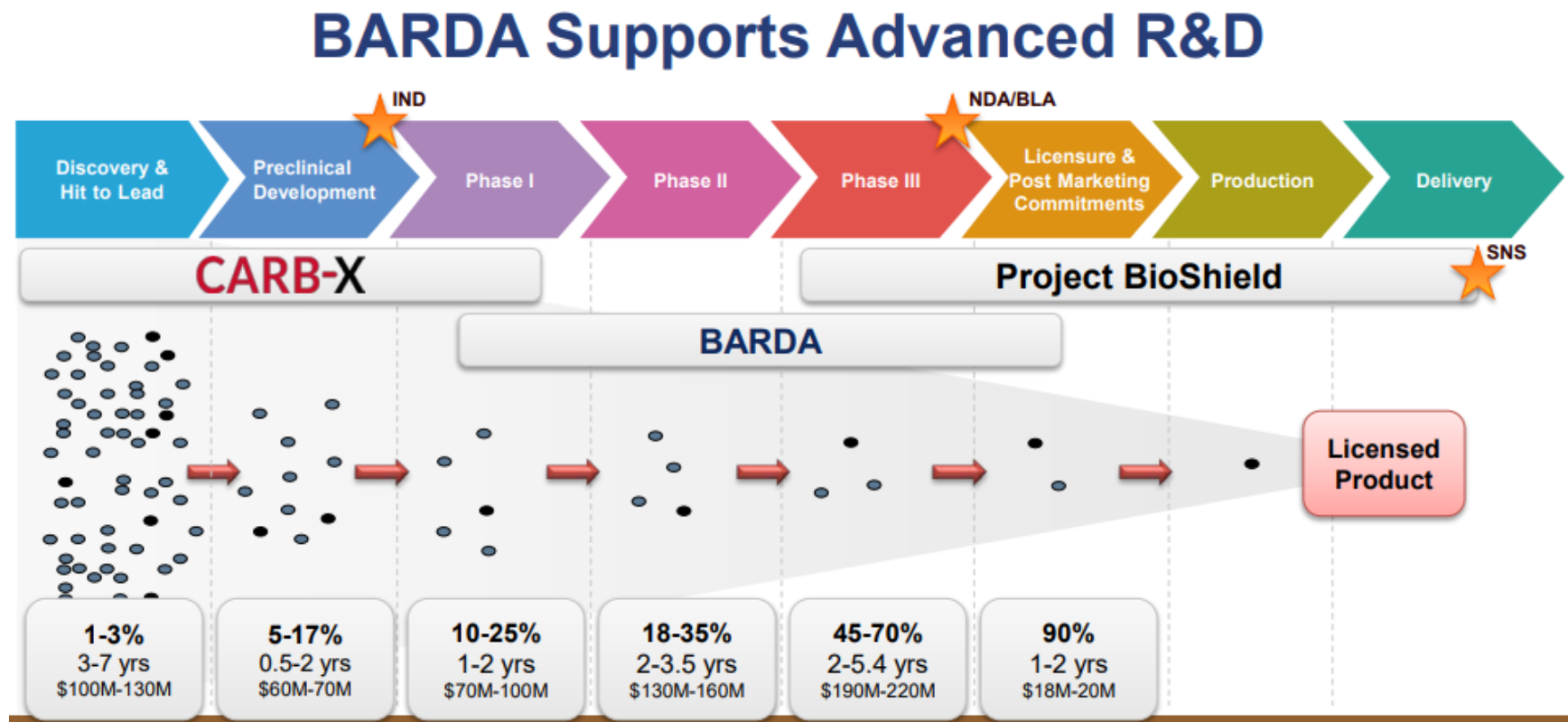
- ▶ Initial focus on biodefense, now with broader scope against AMR pathogens





# Push incentive - BARDA

- ▶ Supports various R&D programs at various stages



[Our advice for clinicians on the coronavirus is here.](#)

If you are a member of the public looking for information and advice about coronavirus (COVID-19), including information about the COVID-19 vaccine, go to the [NHS website](#). You can also find guidance and support on the [GOV.UK website](#).

## Blog

### How the 'NHS model' to tackle antimicrobial resistance (AMR) can set a global standard

 18 December 2020  [Mark Perkins and David Glover](#)

Medicine

**NHS England and Improvement, in collaboration with the National Institute for Health and Care Excellence (NICE) and the Department of Health and Social Care (DHSC), has selected the first antimicrobial drugs to be purchased via the UK's innovative 'subscription-type' payment model.**

**NHS England and Improvement project leads, Mark Perkins and David Glover, discuss this important step in tackling antimicrobial resistance (AMR).**

### Latest posts

[Advice for parents, guardians and carers on how to support a child or young person if you're concerned about their mental health](#)

[What to do if you're a young person and it's all getting too much](#)

[Community pharmacies to be at the forefront of NHS efforts to save lives](#)



# Pull incentive – UK model

- ▶ **Expected health benefits of new antimicrobials**
  - ▶ Spectrum
  - ▶ Transmission
  - ▶ Enablement
  - ▶ Diversity
  - ▶ Insurance
- ▶ **Selection criteria**
  - ▶ Degree of novelty of the product, surety of supply, antimicrobial stewardship and manufacturing practices, antimicrobial surveillance, cost
  - ▶ Two agents made finalists – ceftazidime-avibactam and cefiderocol

# Pull incentive – Japan model

新規

## 抗菌薬確保支援事業

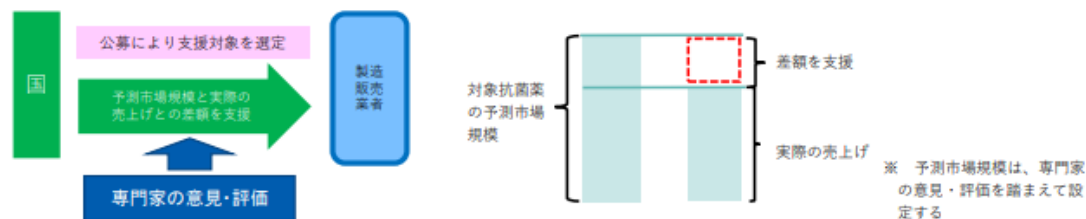
令和5年度当初予算案 11億円 (一) ※(一)内は前年度当初予算額

### 1 背景

- 薬剤耐性 (AMR) による死者数は今後増大するとされている。 (※1)  
(※1) AMRに起因する死亡者数は低く見積もって世界で70万人。何も対策を取らない場合 (耐性率が現在のペースで増加した場合)、2050年には1,000万人の死亡が想定されている。  
(Antimicrobial Resistance in G7 Countries and Beyond, G7 OECD report, Sept. 2015)
- 耐性菌に対する新たに承認された抗菌薬の数は近年減少傾向である。 (※2)  
(※2) 日本の抗菌薬の承認数は1990年～1999年27剤、2000年～2009年16剤、2010年～2019年11剤。
- 新規抗菌薬の開発には、多額の費用を要するが、高い薬価がつかないなど収益性が低いこと、また、使用量を適正な水準にコントロールすることが求められる抗菌薬の特性 (※3) による販売での制約といった収益見込みの低さから、製薬企業の参入ハードルは高くなっている。  
(※3) 抗菌薬が必要でない病態に投与するなどの不必要な使用や投与量・投与期間が標準的な治療から逸脱した不適切な使用を行うと、耐性菌が増加し、結果として抗菌薬が使用できなくなる。
- 2021年にイギリスで開催されたG7の保健財務大臣会合では市場インセンティブについて議論を行い、実施を各国に強く呼びかけた。
- 現在、スウェーデン、英国で市場インセンティブの試行プロジェクトが進行中である。(他に米国が現在検討している。)

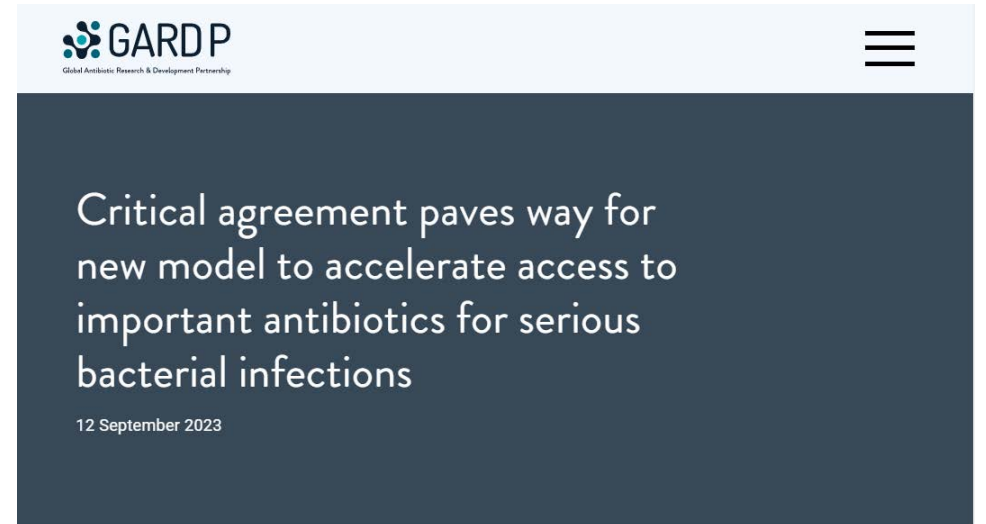
### 2 事業の概要・スキーム

- 我が国においても、抗菌薬による治療環境を維持しつつ、国際保健に関する国際的な議論で主導的な役割を果たすため、市場インセンティブのモデル事業 (企業が国の薬剤耐性対策 (販売量の適正水準維持) に協力することで生じる減収に対して、一定額の収入を国が支援すると同時に、抗菌薬の開発を促す仕組み) を実施する。
- 支援対象として、公衆衛生上脅威となる薬剤耐性菌の治療薬を選定し、日本における市場インセンティブの実現可能性を具体的に検証することを目標とする。
- 抗菌薬の適正使用を保ちつつ、新規抗菌薬の開発を促進し、耐性菌の治療の選択肢を確保することに資する。



# Addressing global access

- ▶ License and technology transfer of cefiderocol to GARDP (Global Antibiotic Research and Development Partnership)
- ▶ The drug will become accessible to patients in India and beyond through a local manufacturer (Orchid Pharma)
- ▶ Provisions to strengthen hospital-based stewardship



Osaka (Japan), Chennai (India), Geneva (Switzerland), Boston (USA), 12 September 2023—A new agreement is poised to accelerate antibiotic access for tens of thousands of patients in regions with the highest rates of antimicrobial resistance (AMR). The Global Antibiotic Research & Development Partnership (GARDP) and India-based Orchid Pharma Ltd (Orchid) have signed a sublicense agreement to manufacture cefiderocol, an antibiotic to treat certain Gram-negative infections. This agreement is a critical step in [an ambitious project](#) by Shionogi & Co. Ltd. (Shionogi), GARDP, and the Clinton Health Access Initiative (CHAI) that aims to provide access to cefiderocol in a number of predominantly low- and middle-income countries, pending local authorization or national regulatory approval.

R&D

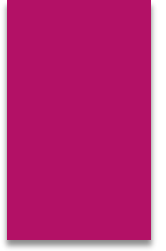
Access

Ensuring future  
availability of  
effective  
antimicrobials

Funding

Stewardship

Surveillance



# Conclusion

- ▶ Antimicrobials save lives and enable modern medicine
- ▶ AMR threatens the utility of existing antimicrobial agents
- ▶ There is an ongoing shortage of pipeline
- ▶ Efforts are under way to support development of new agents
- ▶ Access to effective antimicrobials in LMICs is a global health issue
- ▶ Stewardship needs to be strengthened to ensure their lasting utility



# Thank you



National Institute of  
Allergy and  
Infectious Diseases

