# Antimicrobial Resistance (AMR) - Pipeline

Prepared for the IFPMA

April 2024

# 10 new antibiotics or combinations have been approved since WHO started tracking pipeline data in 2017

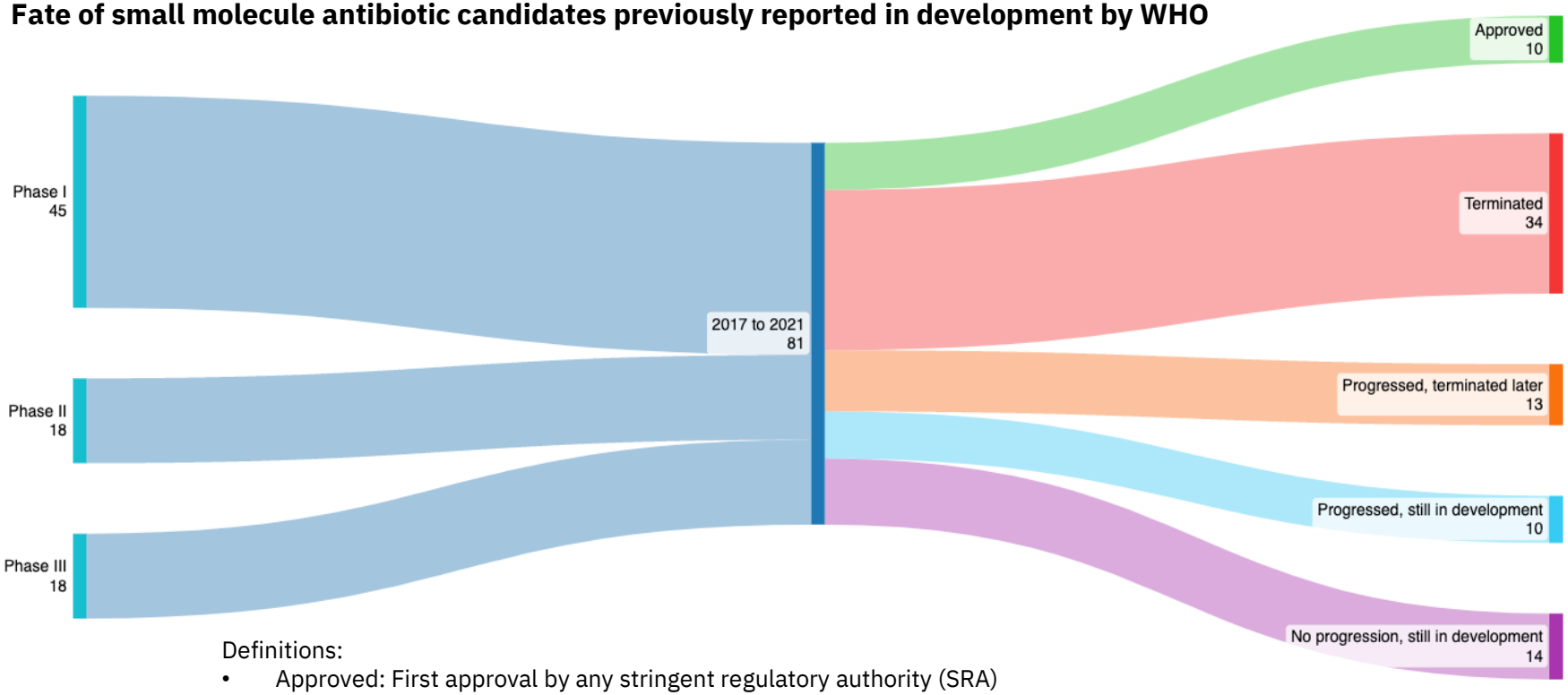
Overview of the fate of assets in the priority antibiotic pipeline, WHO pipeline data from 2017 to 2021, tracked through early 2024

Limitations/approach:

→ Does not include clinical-stage antibiotics in the pipeline that have been repurposed. Candidates are only counted once if trialled/approved in multiple indications.

→ Includes only first approvals by stringent regulatory authorities (SRAs). Fixed-dose combinations are only included if at least one entity is new.

## Fate of small molecule antibiotic candidates previously reported in development by WHO




An additional **31 non-traditional candidates** (12 Phase I, 14 Phase II, 5 Phase III) were in the clinical development pipeline as of 2021, but have not been included in this analysis. SER-109, a non-traditional candidate for *C. difficile*, was also approved in 2023.

**Note:** Does not include TB candidates

The right-hand side of the graph displays the status of assets seen in the WHO clinical pipeline reviews up to 2022 (2021 data) **as of early 2024.**

Definitions:

- Approved: First approval by any stringent regulatory authority (SRA)
- Progressed, terminated later: Advanced to later clinical phase than when first reported but was later terminated
- Progressed, still in development: Progressed to later clinical phase than when first reported
- No progression, still in development: Still in the same phase of development as when first reported

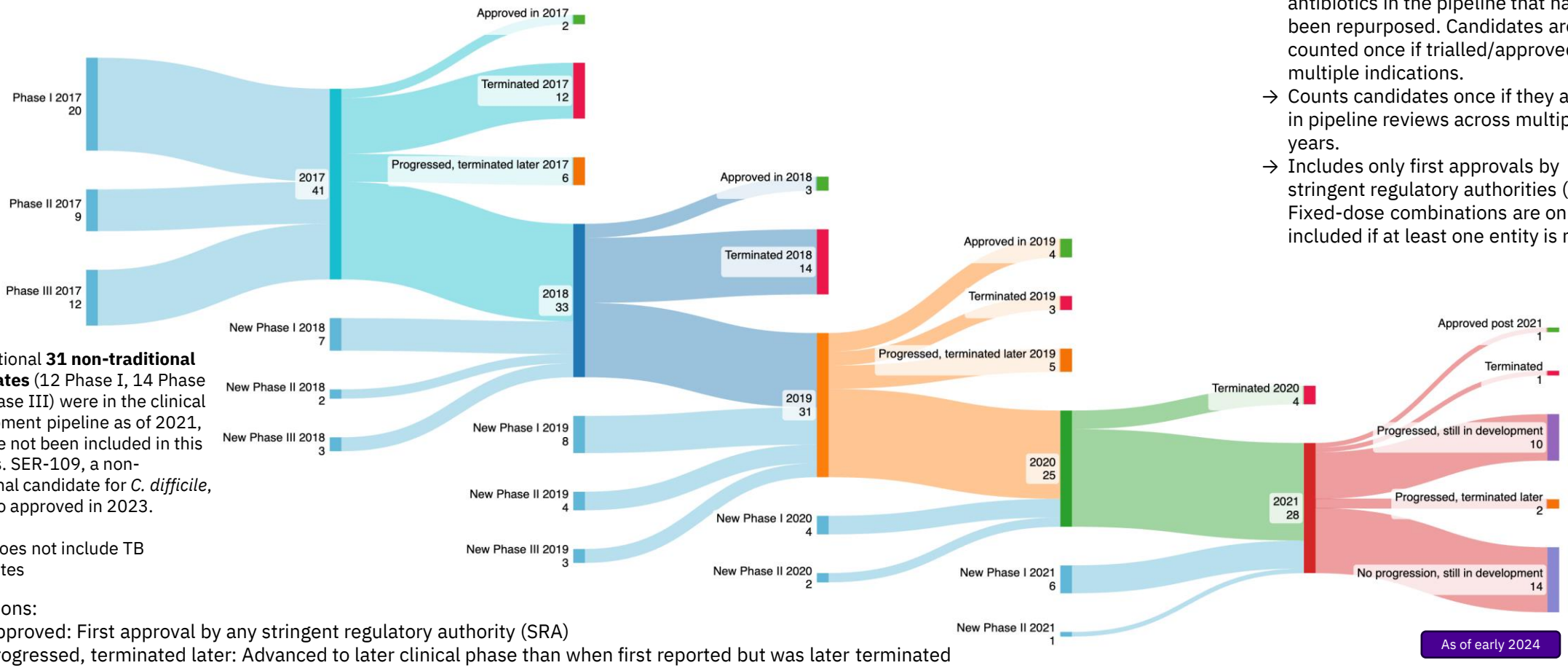


Data: Airfinity, WHO
Visualisation: Airfinity

# The number of antibiotics entering clinical trials has stagnated in recent years, with few continuing to late phase

Overview of the fate of assets in the priority antibiotic pipeline, WHO pipeline data from 2017 to 2021, tracked through early 2024

## Fate of small molecule antibiotic candidates in development by year and phase

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**Note:** Does not include TB candidates

Limitations/approach:

→ Does not include clinical-stage antibiotics in the pipeline that have been repurposed. Candidates are only counted once if trialled/approved in multiple indications.

→ Counts candidates once if they appear in pipeline reviews across multiple years.

→ Includes only first approvals by stringent regulatory authorities (SRAs). Fixed-dose combinations are only included if at least one entity is new.

Definitions:

- Approved: First approval by any stringent regulatory authority (SRA)
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- No progression, still in development: Still in the same phase of development as when first reported

Final breakdown of the graph displays the status of assets seen in the WHO clinical pipeline review in 2022 (2021 data) **as of early 2024.**

Data: Airfinity, WHO
Visualisation: Airfinity

# There have been only 2 approvals for molecules defined by the WHO as innovative (based on class, target, mode of action)

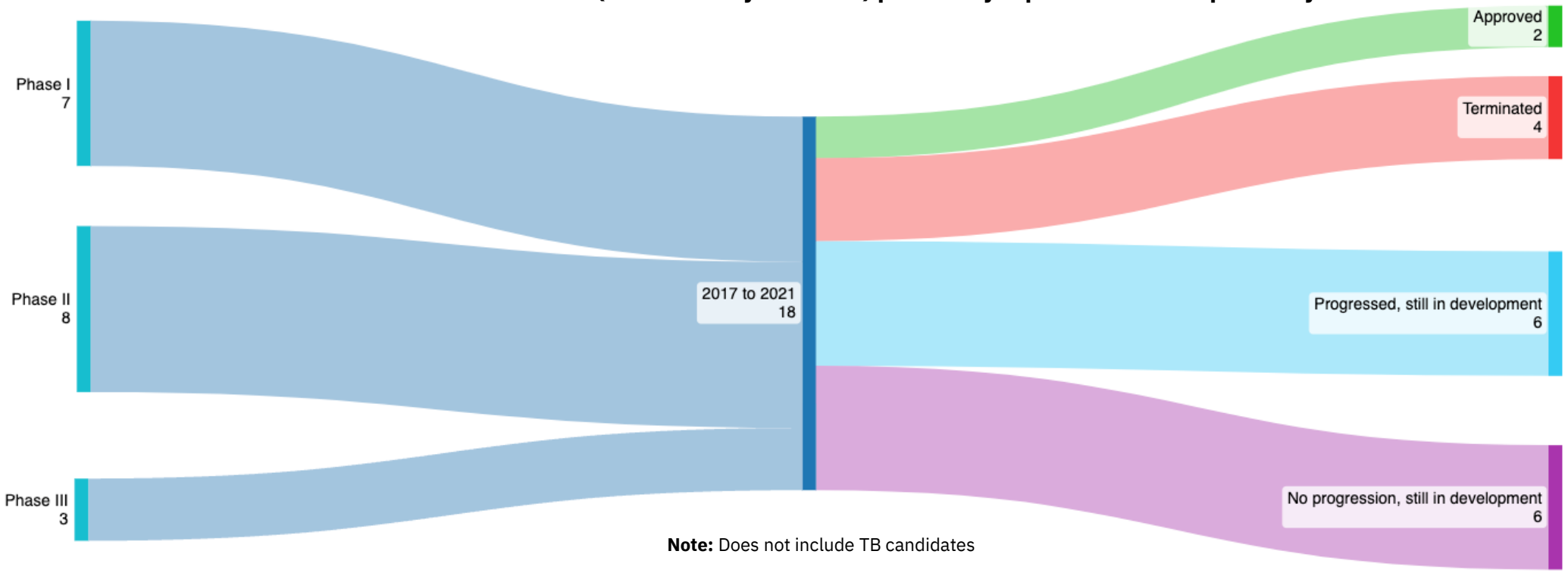
Overview of the fate of assets in the priority antibiotic pipeline, WHO pipeline data from 2017 to 2021, tracked through early 2024

Limitations/approach:

→ Candidates are only counted once if trialled/approved in multiple indications.

→ Includes only first approvals by stringent regulatory authorities (SRAs). Fixed-dose combinations are only included if at least one entity is new.

## Fate of innovative antibiotics (as defined by the WHO) previously reported in development by WHO




**Note:** Does not include TB candidates

**WHO definition of innovative antibiotics**

Requires at least one of 4 criteria:

- New chemical class
- New target
- New mode of action, and/or no cross-resistance to other antibiotic classes

The right-hand side of the graph displays the status of assets seen in the WHO clinical pipeline reviews up to 2022 (2021 data) **as of early 2024.**

Definitions:

- Approved: First approval by any stringent regulatory authority (SRA)
- Progressed, terminated later: Advanced to later clinical phase than when first reported but was later terminated
- Progressed, still in development: Progressed to later clinical phase than when first reported
- No progression, still in development: Still in the same phase of development as when first reported



Data: Airfinity, WHO
Visualisation: Airfinity

# There have been 10 total approvals* by SRAs of candidate antibiotics seen in WHO clinical development pipeline reports

Limitations/approach:
→ Includes only first approvals by stringent regulatory authorities (SRAs). Fixed-dose combinations are only included if at least one entity is new.

## Small molecule antibiotic SRA approvals for candidates previously reported in development by WHO

| Candidate (developer) | WHO Innovative (Yes/No/NA) | Alternative Names | First Approval | Pre-approval funding sources and known licensing agreements | Developer fate/current status |
|---|---|---|---|---|---|
| **Cefiderocol (Shionogi)** | **N/A** | S-649266, GSK-2696266, | Approved by FDA November 2019 | Post-approval licensing agreement with GARDP | Still active. |
| **Lefamulin (Nabriva)** | **Yes** | BC-3781 | Approved by FDA Aug 2019 | Venture funding, IPO | Still active. |
| **Relebactam + imipenem/cilastatin (MSD)** | **No** | MK-7655, Recarbrio | Approved by FDA 2019 | N/A | Still active. |
| **Eravacycline (Tetraphase)** | **No** | TP-434 | Approved by FDA Aug 2018 | Venture funding, CARB-X, BARDA, IPO | Tetraphase bought by La Jolla in 2020. La Jolla purchased by Innoviva in 2022. Both purchases distressed sales at low value. |
| **Lascufloxacin (Kyorin)** | **No** | KRP-AM1977 | Approved in Japan 2019 | Unclear | Still active. |
| **Plazomicin (Achaogen)** | **No** | ACHN-490 | Approved by FDA June 2018 | Venture, funding, CARB-X, BARDA, IPO | Achaogen bankrupt in 2019, assets bought by Cipla for $16M in June 2019. Distressed sale at low value. |
| **Omadacycline (Paratek)** | **No** | – | Approved by FDA October 2018 | Venture funding, BARDA, IPO | Still active. Acquired by Novo Holdings in September 2023. |
| **Delafloxacin (Melinta Therapeutics)** | **No** | Baxdela | Approved by FDA June 2017 | Venture funding, CARB-X, IPO | Melinta filed for bankruptcy in 2019, taken over by Deerfield Management. Distressed sale at low value. |
| **Vaborbactam + meropenem (Melinta Therapeutics)** | **Yes** | Carbavance | Approved by FDA August 2017 | CARB-X, BARDA, IPO, Private Equity | Melinta filed for bankruptcy in 2019, taken over by Deerfield Management. Distressed sale at low value. |
| **Sulbactam-Durlobactam (Entasis)** | **No** | SUL-DUR, ETX-2514 + sulbactam | Approved by FDA May 2023 | Venture funding, CARB-X, IPO | Still active. Acquired by Innoviva in May 2022. |

*10 direct-acting small molecule antibiotic approvals. SER-109, a non-traditional candidate for *C. difficile*, was also approved in 2023. Excludes TB approvals.

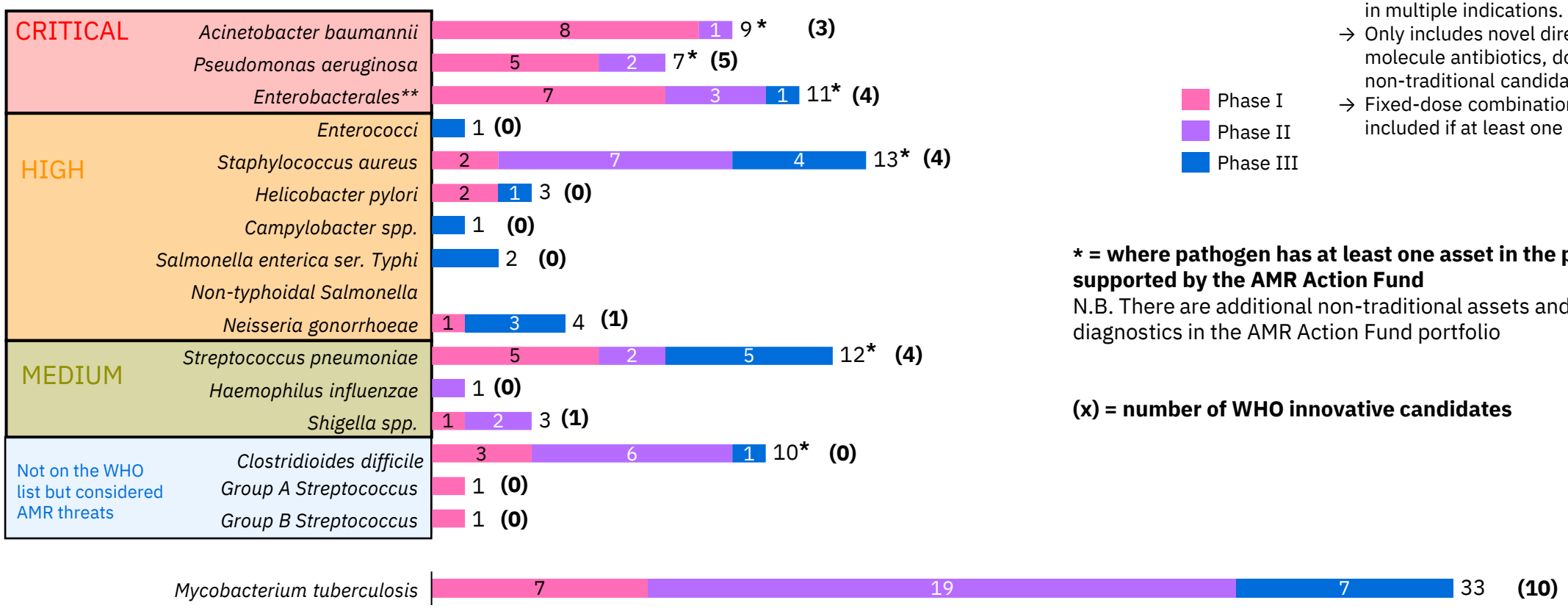


Data: Airfinity, Crunchbase
Visualisation: Airfinity

# Many critical and high-priority bacterial pathogen require further development and stronger pipeline

Overview of clinical candidates in development for priority bacteria by threat level (assigned by the WHO, 2017)

## Clinical small molecule antibiotic candidates in development against priority bacteria by WHO priority




Limitations/approach:

→ In this analysis, some candidates are counted more than once as they target multiple pathogens or are being trialled in multiple indications.

→ Only includes novel direct-acting small molecule antibiotics, does not include non-traditional candidates.

→ Fixed-dose combinations are only included if at least one entity is new.

*** = where pathogen has at least one asset in the pipeline supported by the AMR Action Fund**

N.B. There are additional non-traditional assets and diagnostics in the AMR Action Fund portfolio

**(x) = number of WHO innovative candidates**

**Enterobacterales encompasses both carbapenem-resistant- and ESBL-producing-Enterobacterales, which includes *Escherichia coli* and *Klebsiella pneumoniae*



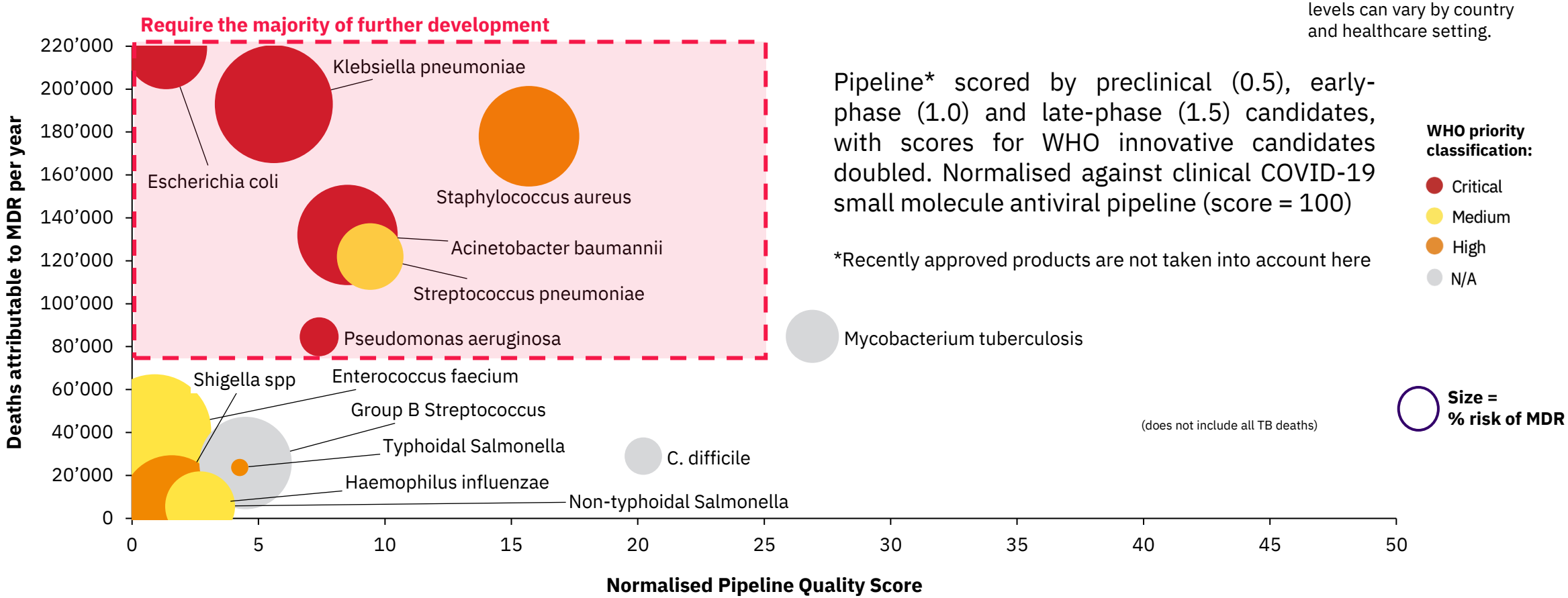
Data: Airfinity
Visualisation: Airfinity

# Bacteria with high multidrug resistance and related deaths require the majority of further treatment development

Overview of estimate of risk of multidrug resistance (MDR) and attributable annual deaths

Limitations/approach:
→ Does not take overall case rates into account.
→ Multidrug resistance (MDR) levels can vary by country and healthcare setting.

**Pipeline score vs multidrug resistance (MDR)-attributable deaths of WHO priority bacterial pathogens**




Pipeline* scored by preclinical (0.5), early-phase (1.0) and late-phase (1.5) candidates, with scores for WHO innovative candidates doubled. Normalised against clinical COVID-19 small molecule antiviral pipeline (score = 100)

*Recently approved products are not taken into account here

**WHO priority classification:**
- Critical
- Medium
- High
- N/A

(does not include all TB deaths)

**Size = % risk of MDR**



Data and visualisation: Airfinity

# The current antibiotic innovation ecosystem is not sufficient to support the development of new antibiotics

## Overview of assumptions for the potential development landscape over the next 10 years without new incentives

Limitations/approach:

→ Based on progression of current pipeline and rate of entry, failure and approval based on observed trends.

### Summary of assumptions for modelling based on current landscape without new incentives

- Starting point assumed to be current antibiotic pipeline.
- Current clinical candidates **less likely to progress through the pipeline** compared to historical assets and compared to a high funding scenario, particularly those produced by small biotechs (~40% Phase I to II progression rate, <40% Phase II to III progression rate). Progression rates based on continuation of decrease seen in relevant BIO reports, for infectious disease NMEs (excluding vaccines and biologics) between 2016 & 2021, attributed in this analysis to a lack of funding.
- **Late–stage candidates less likely to see approval**, compared to current average. Approvals are based on candidates in the current pipeline with funding sources identified with positive clinical results, and consistent with historical clinical trial and approval timelines.
- **Continuation of some new candidates entering clinical pipeline in Phase I** from large pharma, small biotech with levels of financial support (push funding) consistent with current levels, largely from organisations such as CARB-X, BARDA and GARDP, although reduced from around 4 to 6 per year at present to ~3 per year up to 2030, then reducing to ~2 per year due to poor ecosystem (continued entries assumed to be consistent with current rate of candidates with sufficient financial support to initiate phase I). Reduction assumed with small companies in particular unwilling to risk investment in antibiotic development due to low likelihood of reward. Some Phase I failures due to safety. Candidates more likely to get **stuck due to unfavourable market dynamics**, particularly Phase II and III candidates after 2026.
- Average time from Phase I to approval assumed to be ≥8 years.
- Assumes some natural failures, particularly in Phase I and II, due to factors such as safety, lack of efficacy etc. Assets with positive pivotal clinical data have been considered, with lack of funding considered to be the reason for lack of progression of these assets.

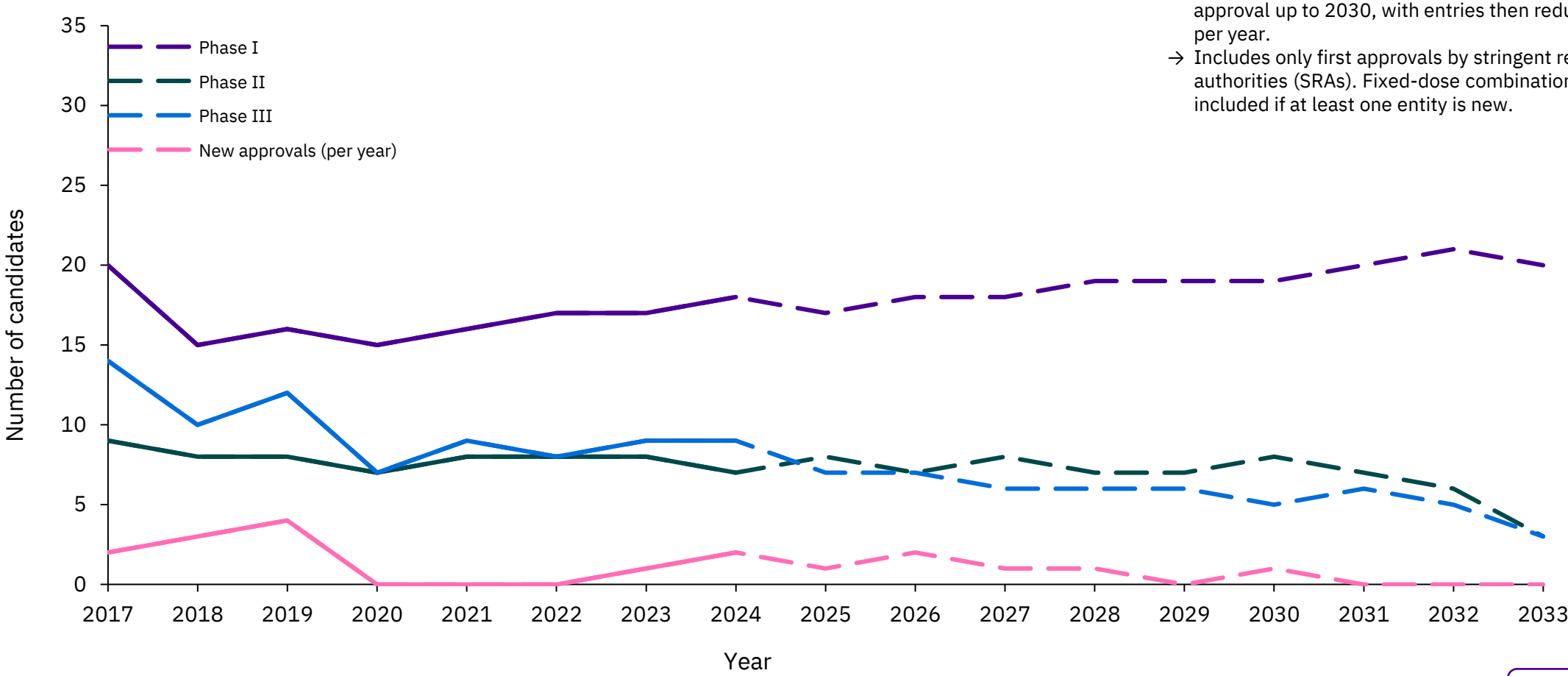


Data: Airfinity, WHO, BIO (2021), BIO (2016)
Visualisation: Airfinity

# Without new incentives, the clinical antibiotic pipeline is likely to further deteriorate

Overview of the potential development landscape over the next 10 years without new incentives

## Potential direct-acting small molecule antibiotic clinical pipeline up to 2033 by phase without new incentives




Limitations/approach:

→ Publicly available information only.

→ Based on progression of current pipeline and consistent rate of entry (3 pear year), failure and approval up to 2030, with entries then reducing to 2 per year.

→ Includes only first approvals by stringent regulatory authorities (SRAs). Fixed-dose combinations are only included if at least one entity is new.



Data: Airfinity
Visualisation: Airfinity

# A “sufficient incentives” scenario would see increased development of clinical stage antibiotics

## Overview of assumptions for the potential development landscape over the next 10 years with sufficient incentives

Limitations/approach:

→ Based on progression of current pipeline and assumption that all clinically relevant assets will see progression with effective incentives.

### Summary of assumptions for modelling based on a pipeline with introduction of sufficient incentives

- Starting point assumed to be current antibiotic pipeline. Assumed that antibiotics targeting **critical and high-priority pathogens will see more development**, with unmet need appropriately recognised in incentive models (as in UK subscription model).
- **Introduction of sufficient incentives from 2025**. Assumes enough financial incentive to attract investment to bring through all candidates currently stuck in development due to unfavourable market conditions, with a particular focus on incentives targeting Phase II and III assets. Assumed that current candidates with positive safety and clinical data from their current/previous phase will progress to the next stage of development.
- Clinical candidates currently stuck in the pipeline with no progression **more likely to progress through the pipeline** than in no new incentives scenario with increased funding (<30% Phase I to II failure rate, <40% Phase II to III failure rate due to clinical efficacy), with progression solely based on positive clinical data. Progression rates for those with no or limited clinical data are based on infectious disease NME (excluding vaccines and biologics) progression rates as reported by the relevant BIO 2021 report.
- Current antibiotics showing efficacy in clinical trials but no progression **likely to move to next phase**, thus contributing to higher overall Phase III to NDA/BLA (>70%) and approval rates.
- **Continuation of new candidates entering clinical pipeline** from large pharma, small biotech with appropriate level of push funding from organisations such as CARB-X, BARDA and GARDP. Overall increased levels of investment leading to ~6 Phase I entries (an increase of ~3 to 4 per year compared to a low-funding scenario) due to the healthier economic landscape initiated by pull incentives. Assumes that all current preclinical candidates in IND-enabling studies with sufficient data will enter phase I, and that this will continue at a consistent rate. Some natural Phase I failures due to safety.
- Average time from Phase I to approval estimated based on Sulbactam-Durlobactam (~7 years).
- Assumes some natural failures, particularly in Phase I and II, due to factors such as safety, lack of efficacy etc. Assumed that all candidates with positive Phase III data in pivotal clinical trials (>300 participants) will see approval, with timelines based on primary completion and/or submission timelines (where available). Timelines for phase II and below based on historical antibiotic approval timelines.

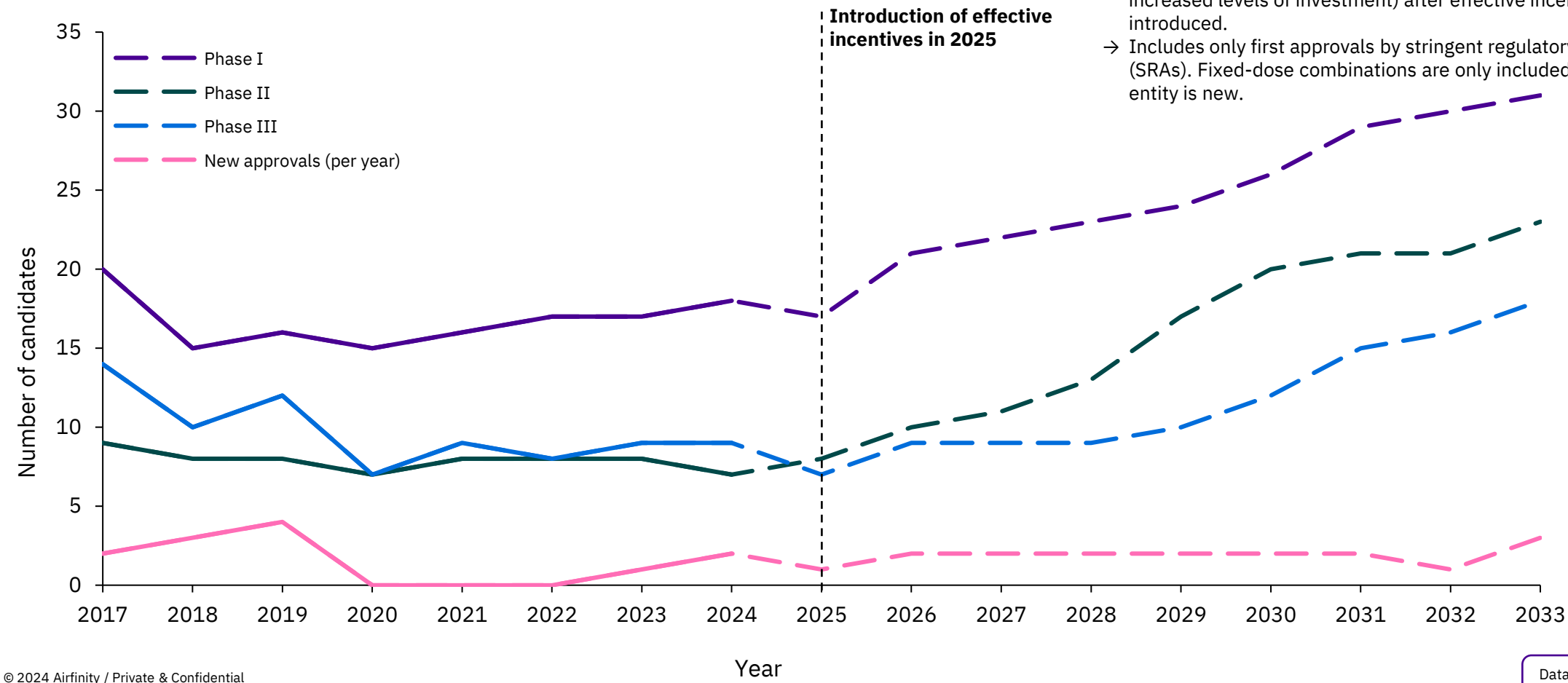


Data: Airfinity, WHO, BIO (2021)
Visualisation: Airfinity

# A “sufficient incentives” scenario in 10 years would have more candidates in all clinical phases, particularly phase III

Overview of the potential development landscape over the next 10 years with sufficient incentives

## Potential direct-acting small molecule antibiotic clinical pipeline up to 2033 by phase with introduction of sufficient incentives




Limitations/approach:

- → Publicly available information only.
- → Based on progression of current pipeline and 6 Phase I entries per year compared to 2-3 in to low-funding scenario (due to overall increased levels of investment) after effective incentives introduced.
- → Includes only first approvals by stringent regulatory authorities (SRAs). Fixed-dose combinations are only included if at least one entity is new.

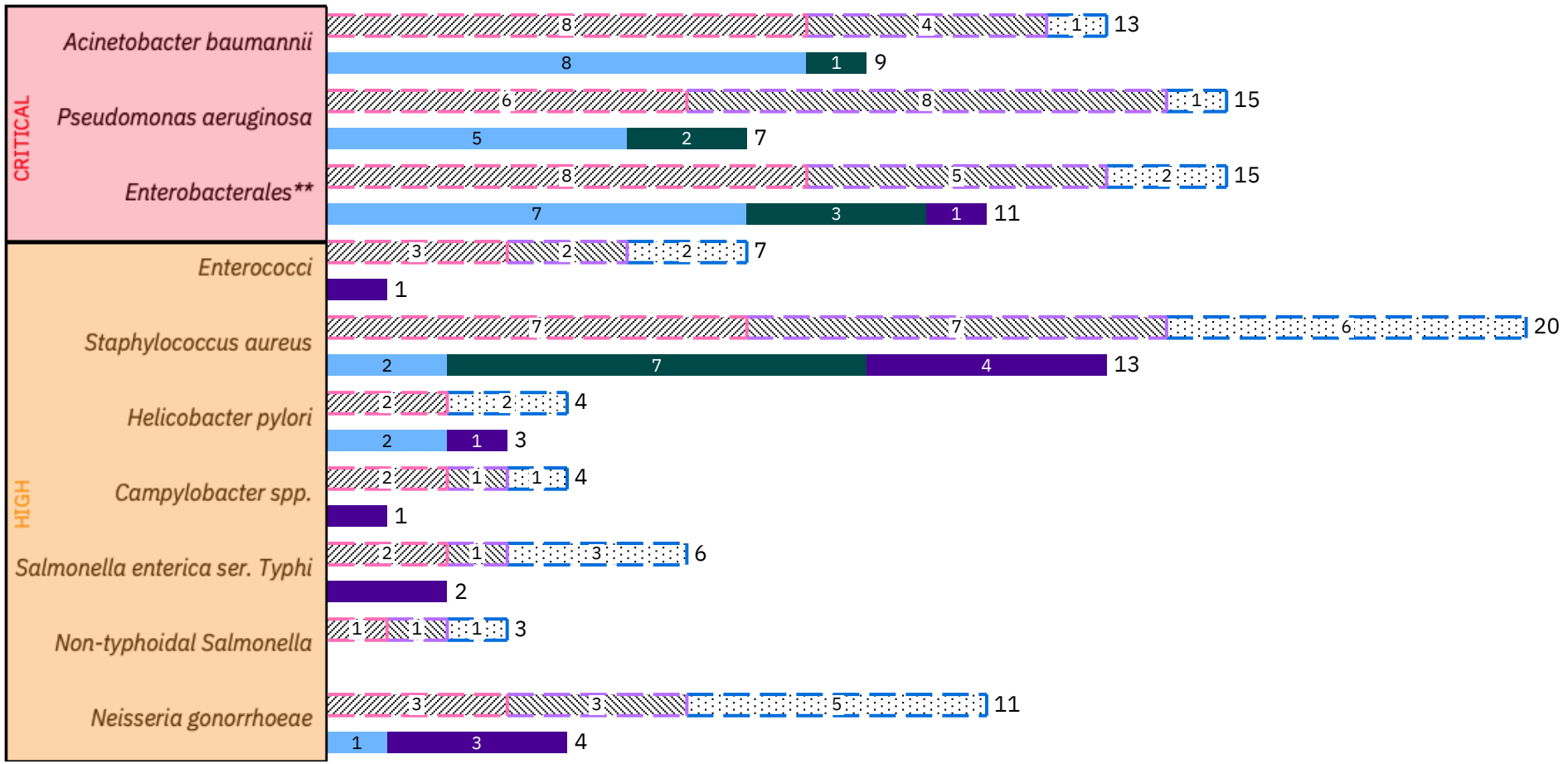


Data: Airfinity
Visualisation: Airfinity

# A “sufficient incentives” scenario pipeline in 10 years would target priority pathogens with high unmet need

Overview of the potential clinical development pipeline in 10 years

## Clinical direct-acting small molecule antibiotic pipeline up to 2033 by pathogen in “sufficient incentives” scenario




Limitations:

→ Publicly available information only.

→ *See further limitations on page 6.*

- Phase I 2033
- Phase II 2033
- Phase III 2033
- Phase I 2023
- Phase II 2023
- Phase III 2023



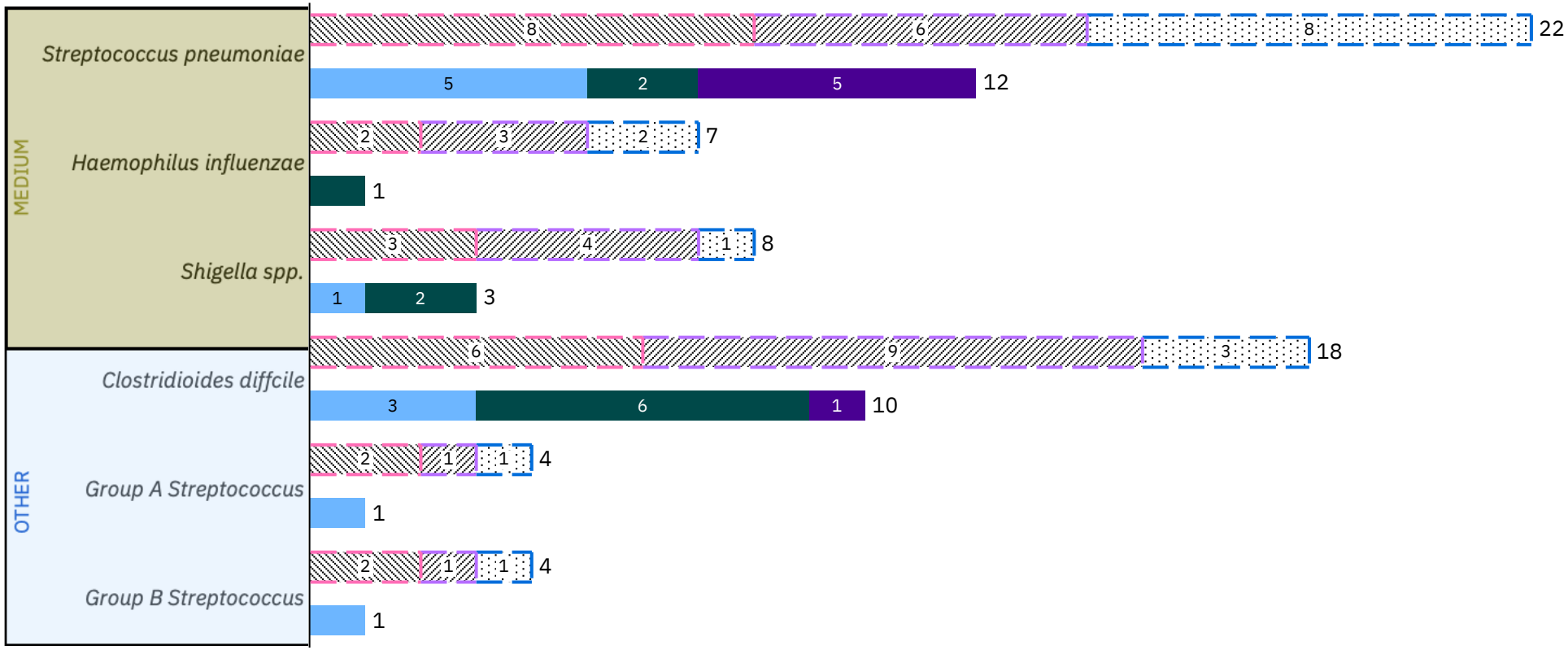
**Enterobacterales encompasses both carbapenem-resistant- and ESBL-producing-Enterobacterales, which includes *Escherichia coli* and *Klebsiella pneumoniae*

Data: Airfinity
Visualisation: Airfinity

# A “sufficient incentives” scenario pipeline in 10 years would target priority pathogens with high unmet need

Overview of the potential clinical development pipeline in 10 years

## Clinical direct-acting small molecule antibiotic pipeline up to 2033 by pathogen in “sufficient incentives” scenario




Limitations:

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→ *See further limitations on page 6.*

- Phase I 2033
- Phase II 2033
- Phase III 2033
- Phase I 2023
- Phase II 2023
- Phase III 2023



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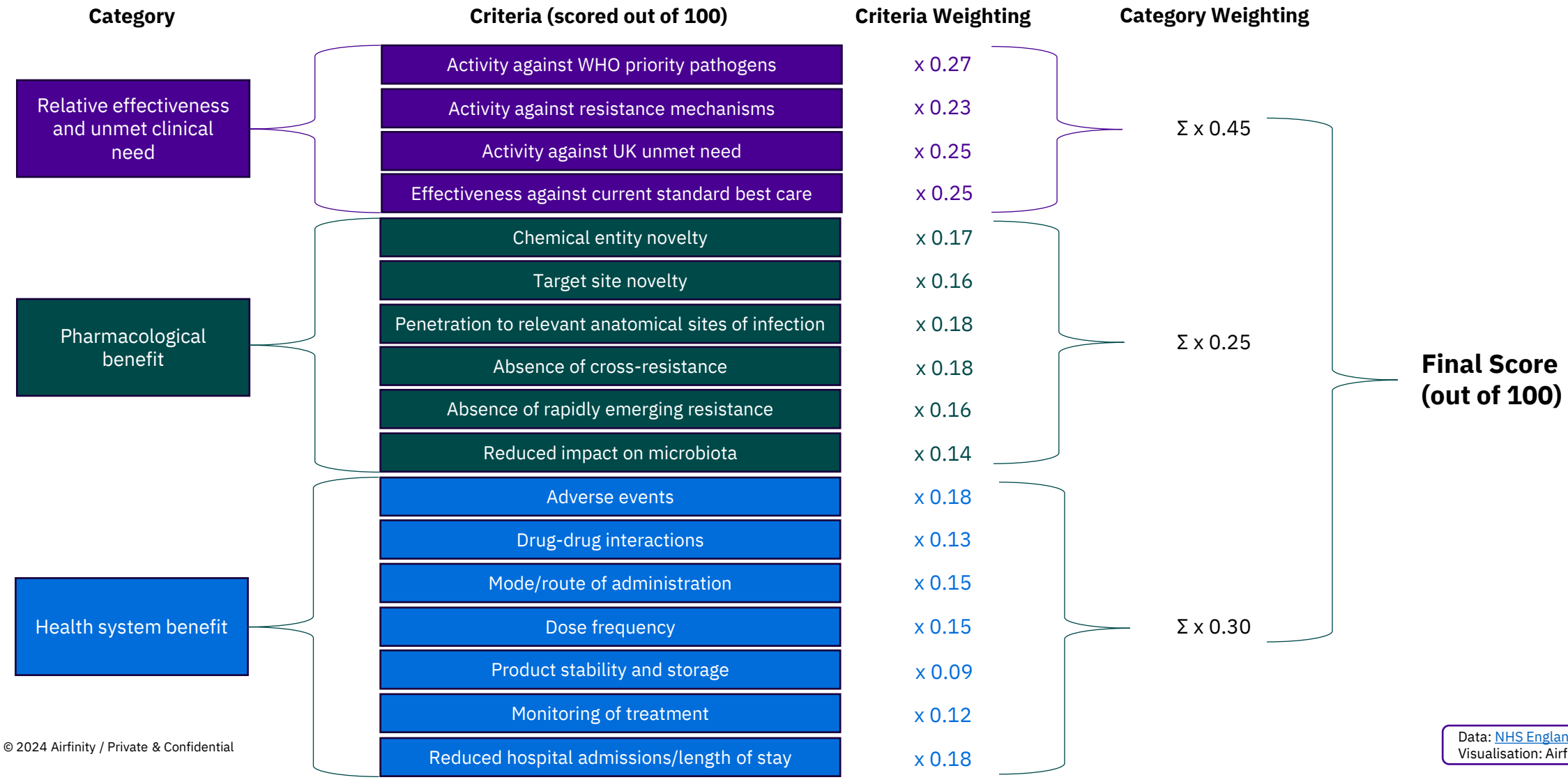
Data: Airfinity
Visualisation: Airfinity

# UK model scores antibiotics on 17 criteria e.g. potential to address unmet need, expanding on WHO's 4 criteria

Overview of NHS England Antimicrobial Subscription Product Award Criteria & Scoring






Data: NHS England
Visualisation: Airfinity

# For a score of 100, an antibiotic would target a critical priority pathogen via a new target and be superior to SOC

## Overview of NHS England Antimicrobial Subscription Product Award Criteria

| | | |
|---|---|---|
| Relative effectiveness and unmet clinical need | Activity against WHO priority pathogens | Higher score given for critical-priority pathogens, e.g. *Enterobacterales* |
| | Activity against resistance mechanisms | Higher score given for activity against key resistances (e.g. MBLs) |
| | Activity against UK unmet need | Based on population morbidity and mortality burden (e.g. MDR bloodstream infections) |
| | Effectiveness against current standard best care | Requires RCT evidence of superiority against current SOC |
| Pharmacological benefit | Chemical entity novelty | New chemical class |
| | Target site novelty | Novel active site not targeted by current antimicrobials |
| | Penetration to relevant anatomical sites of infection | Penetration to relevant sites with drug concentrations at least 4-fold resistance breakpoint |
| | Absence of cross-resistance | No known cross-resistance |
| | Absence of rapidly emerging resistance | No known resistant isolates detected at point of assessment in RCT or lab |
| | Reduced impact on microbiota | Reduces collateral damage – comparators in microbiology-directed treatment have broader spectrum of activity |
| Health system benefit | Adverse events | Rare or very rare serious adverse events |
| | Drug-drug interactions | No clinically significant drug-drug interactions |
| | Mode/route of administration | Delivers step-change improvement (e.g. delivered via inhalation, reduction in infusion time, improved feasibility for outpatient/home IV administration) |
| | Dose frequency | Single or weekly dosing, no observed increase in AMR due to reduced dosing frequency |
| | Product stability and storage | Ready to use with long expiry, no special storage requirements |
| | Monitoring of treatment | No drug and/or serum monitoring required |
| | Reduced hospital admissions/length of stay | Reduced stay or averted admission compared to SOC |

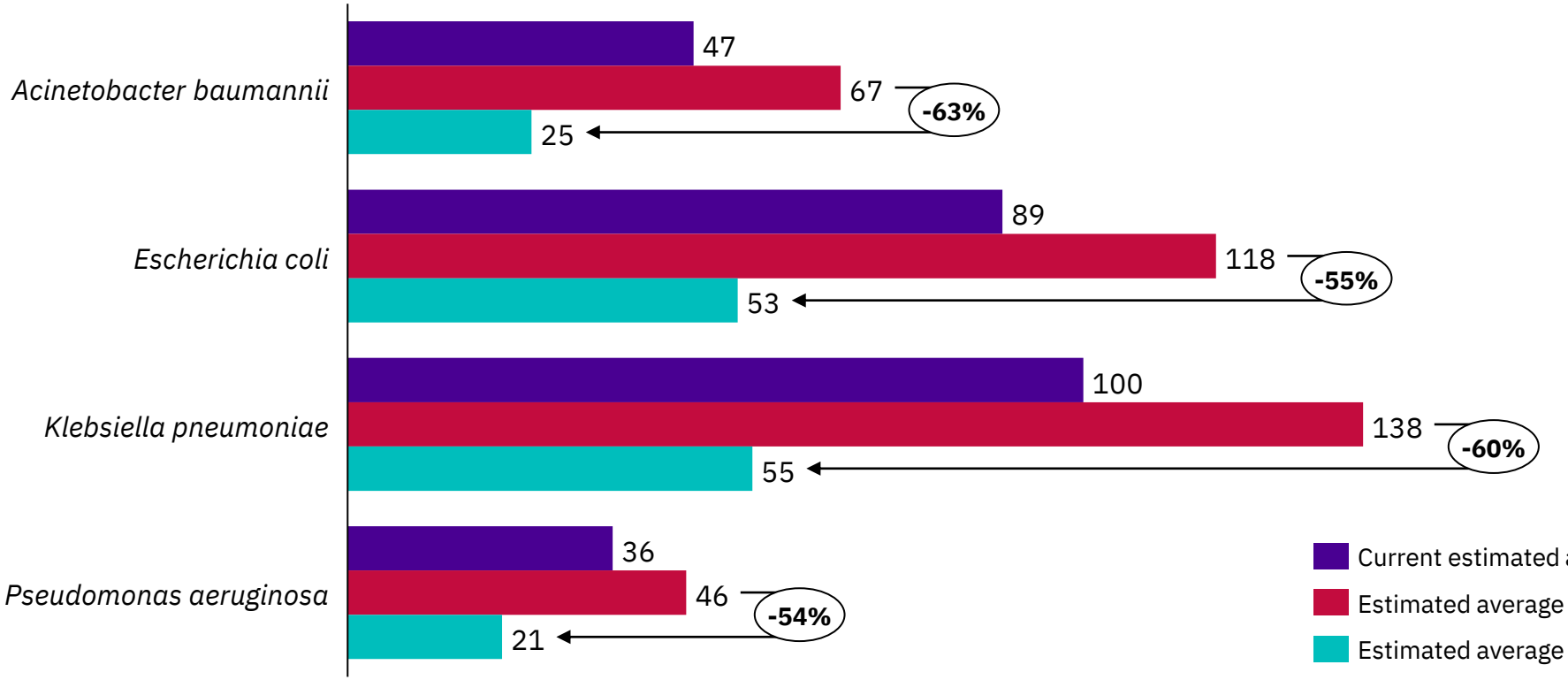


Data: NHS England
Visualisation: Airfinity

# A more robust pipeline would lead to more approvals, reducing potential burden in HICs in the next 10 years by up to 63%

Overview of potential burden in HICs (estimated DALYs) of critical priority bacteria with and without new antibiotics in the next 10 years

**Potential average burden (estimated average DALYs per 100,000) of critical priority bacteria in High Income Countries (HICs) in 10 years with and without new antibiotics**




Limitations:
→ Publicly available information only.

**Note:** burden assessed as an average of all resistances associated with each pathogen.

Impact on HICs assessed in isolation due to data and model limitations. However, similar impact ~~is~~ would be expected globally.

The modelling of DALY growth up until 2033 under the "no new antibiotics" assumption is based on the continuation of current trends in resistant cases and mortality increase. Under the "new antibiotics" assumption, we apply a consistent reduction to the current burden of resistance based on reported effectiveness from available clinical trial data, and/or real-world data from recently approved antibiotics. The model does not consider differences between different syndromic infections and assumes new antibiotics remain fully effective throughout the period studied.



Data: Airfinity, The Lancet
Visualisation: Airfinity

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# More info.


→ Dr Thomas Maguire
tom@airfinity.com

→ Dr Arsalan Azad
arsalan@airfinity.com

→ Konstantin Hardenberg
konstantin@airfinity.com