The antibiotic Research & Development and Access chain

This material was developed in relation to the High-level meeting on AMR in Stockholm 6-7 March 2023.

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sweden 2023.eu Swedish Presidency of the Council of the European Union

High-Level Meeting on Antimicrobial Resistance 6–7 March 2023

The antibiotic Research & Development and Access chain

Background
This material was developed by the Swedish Ministry of Health and Social Affairs in collaboration with ReAct – Action on antibiotic resistance, and Professor Enrico Baraldi, Uppsala University. It was presented at the High-Level Meeting on Antimicrobial Resistance at 6-7 March 2023 during the Swedish Presidency of the Council of the European Union.

The solutions in this material (pages 6-7) were suggested by participants in the expert meeting in connection to the high-level meeting.

Contact the Swedish Ministry of Health and Social Affairs if you wish to receive the presentation as a ppt.-file.
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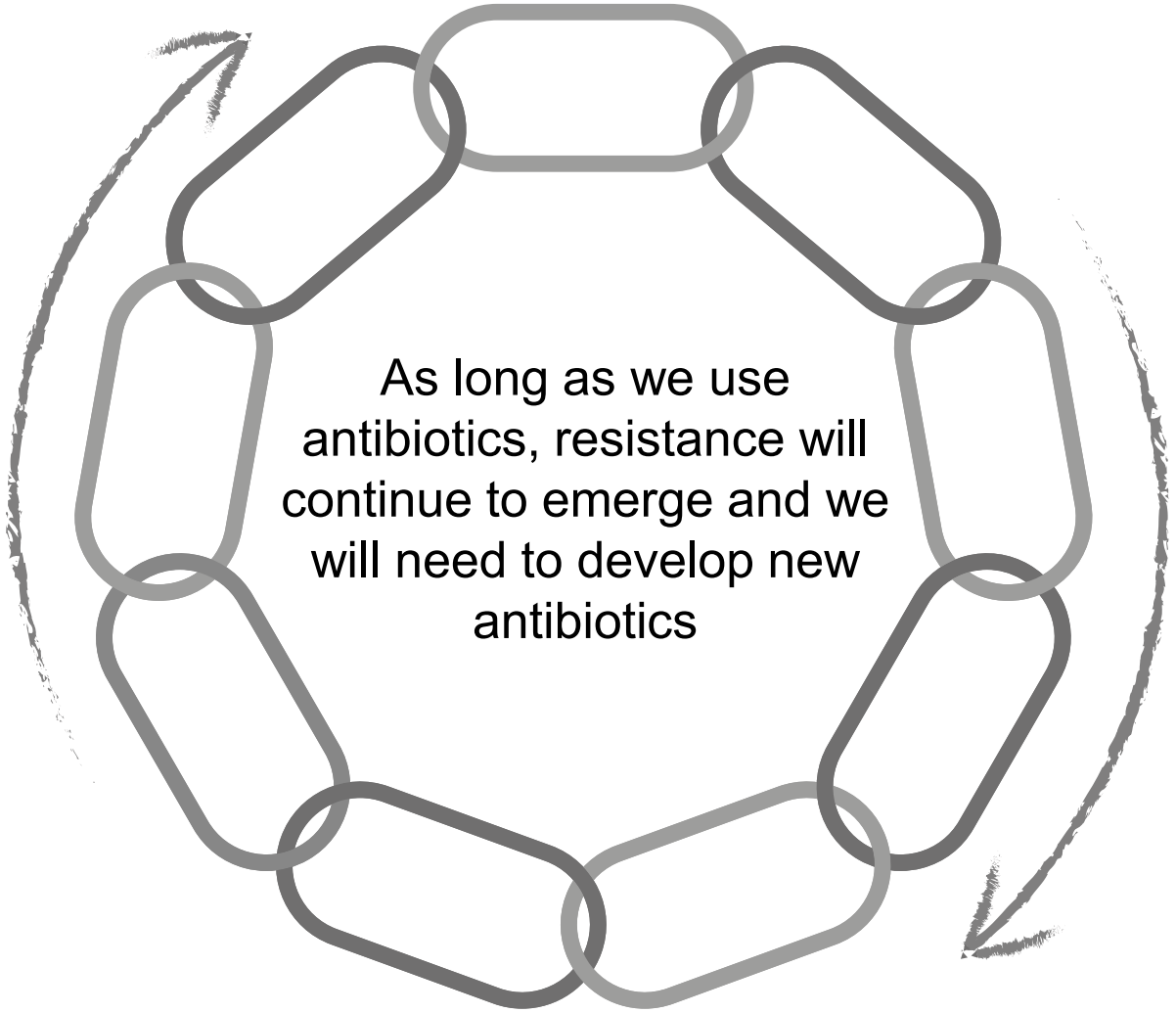
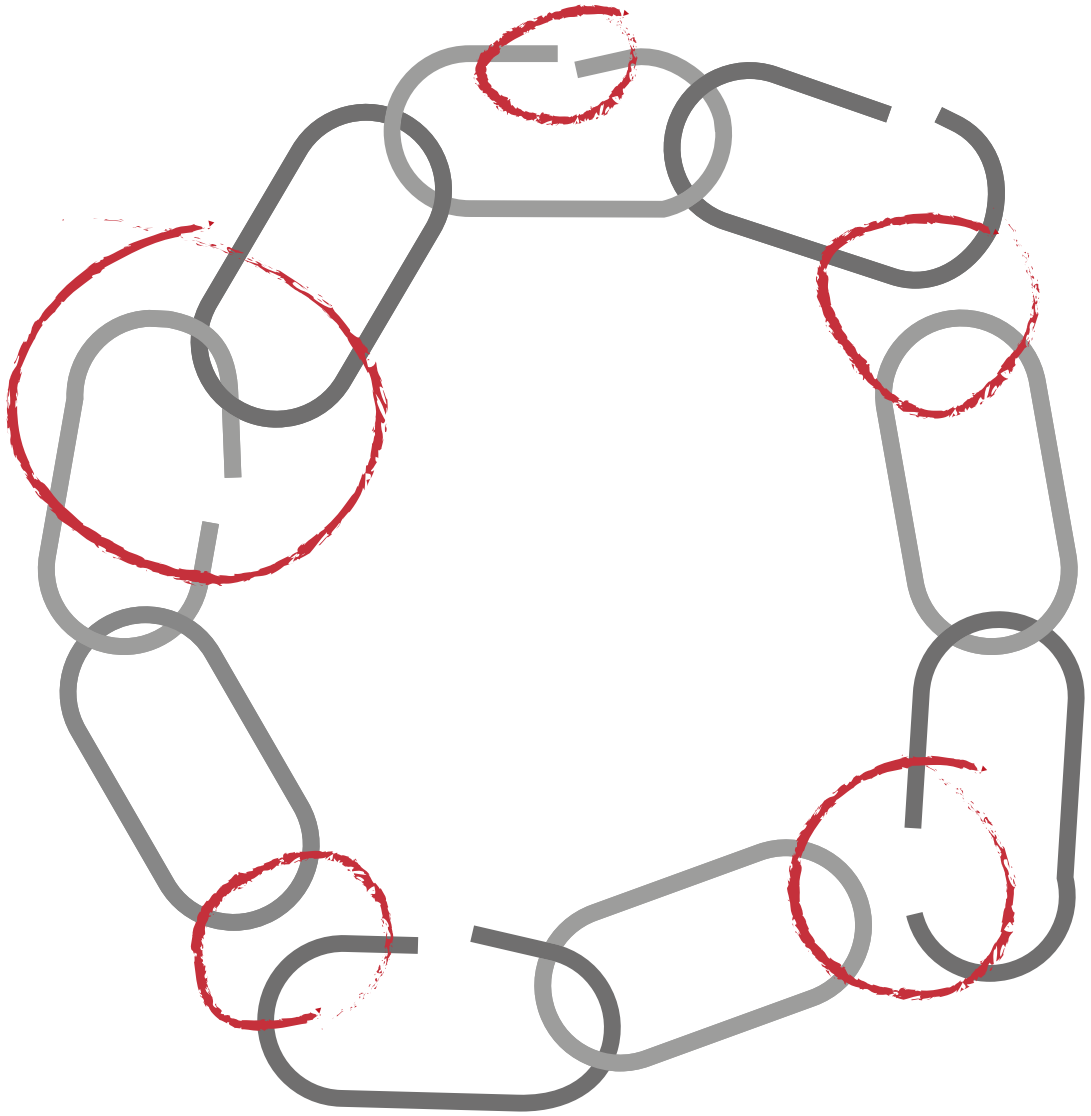
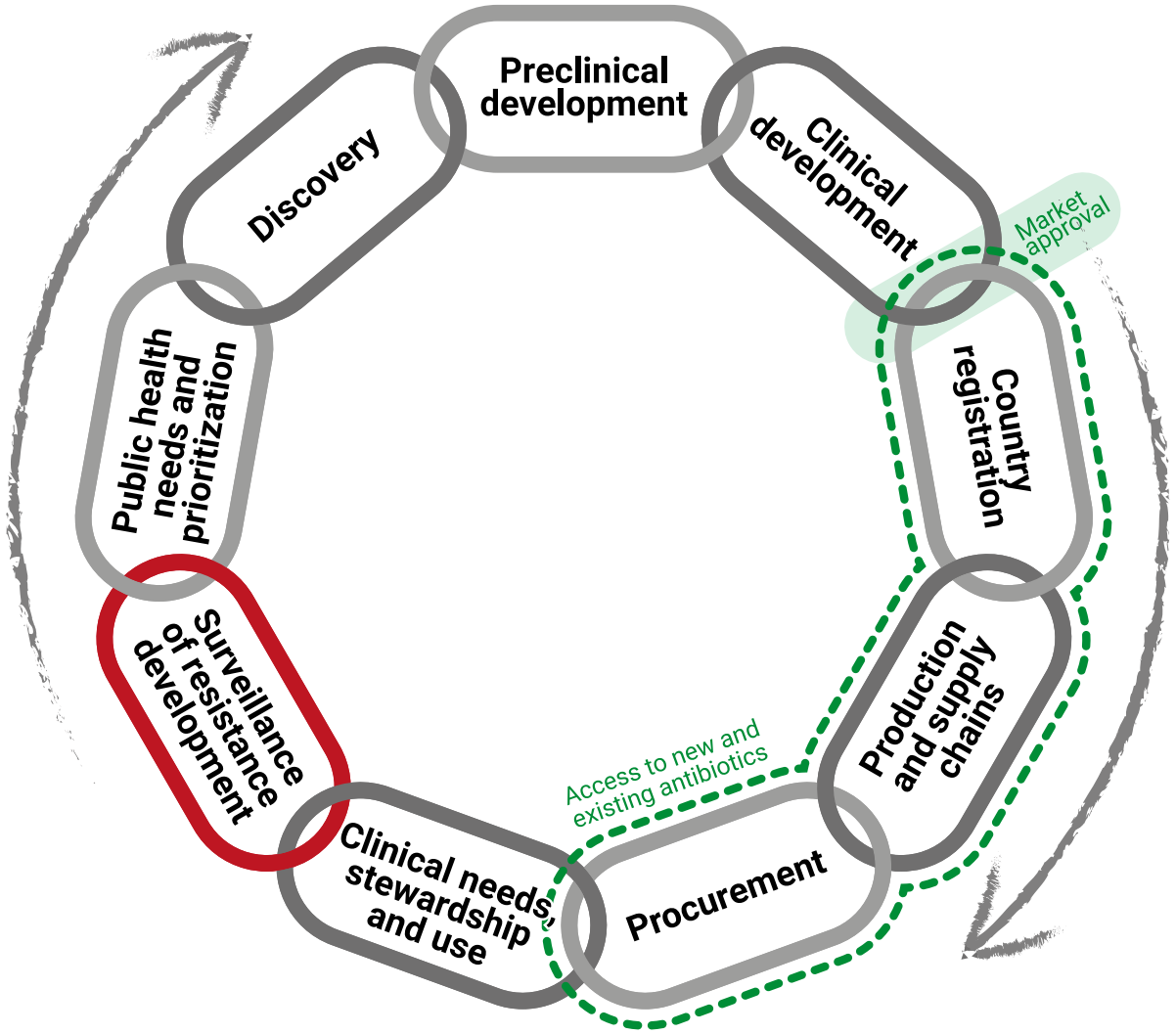
The antibiotic Research & Development and Access chain



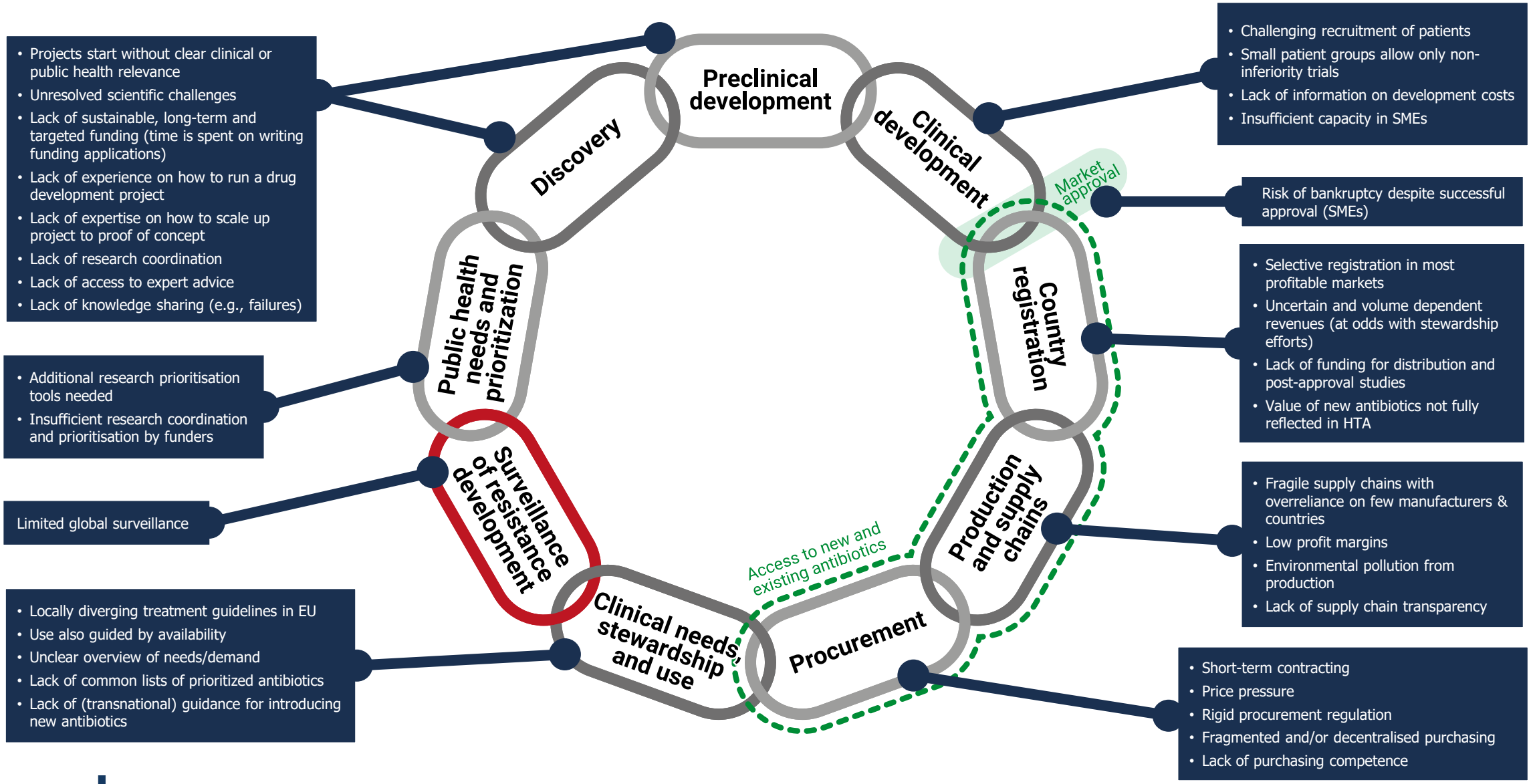
The fragmented antibiotic Research & Development and Access chain



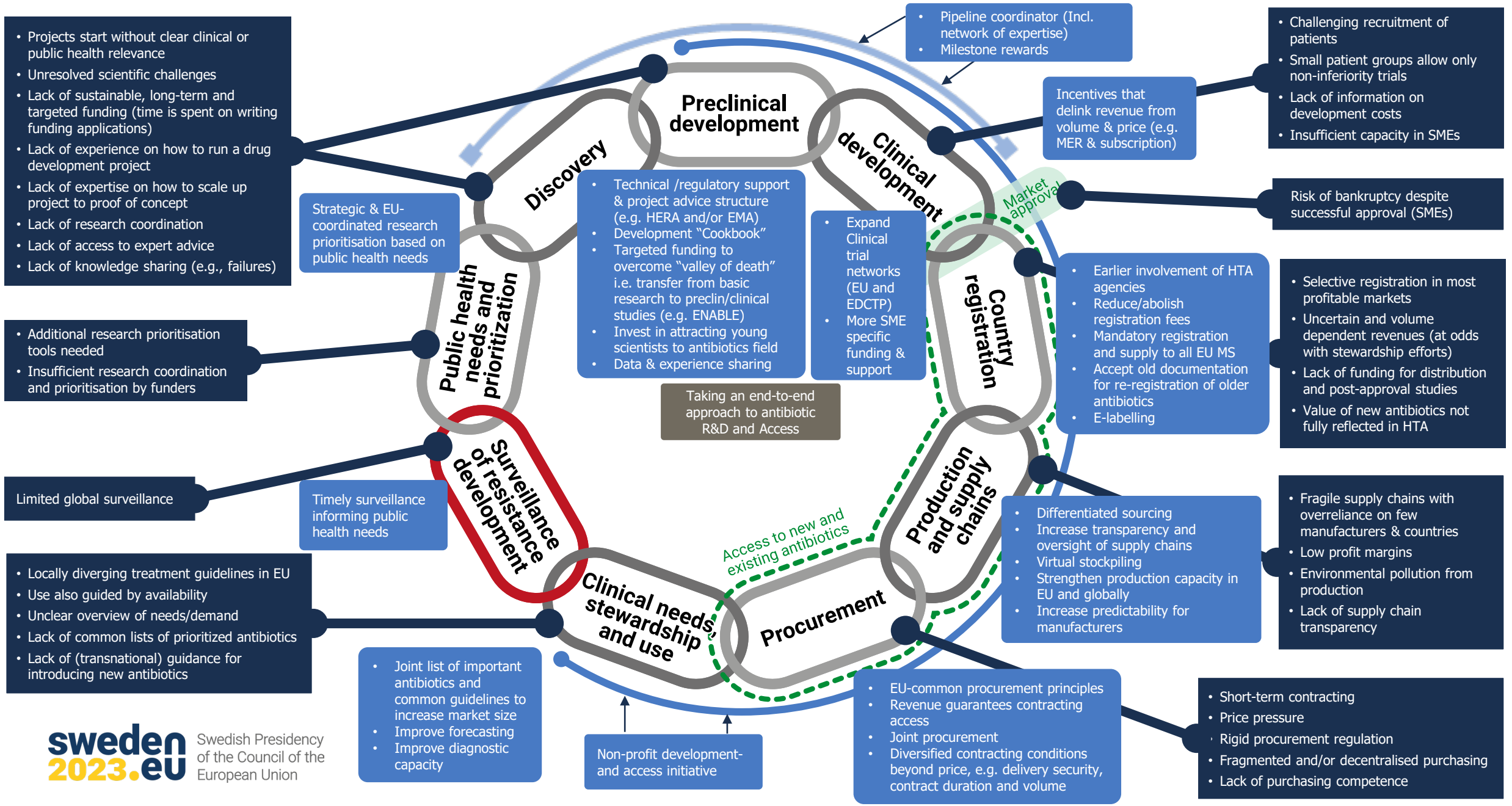
The antibiotic Research & Development and Access chain



Challenges to connecting the links in the chain



Challenges to connecting the links in the chain and suggested solutions



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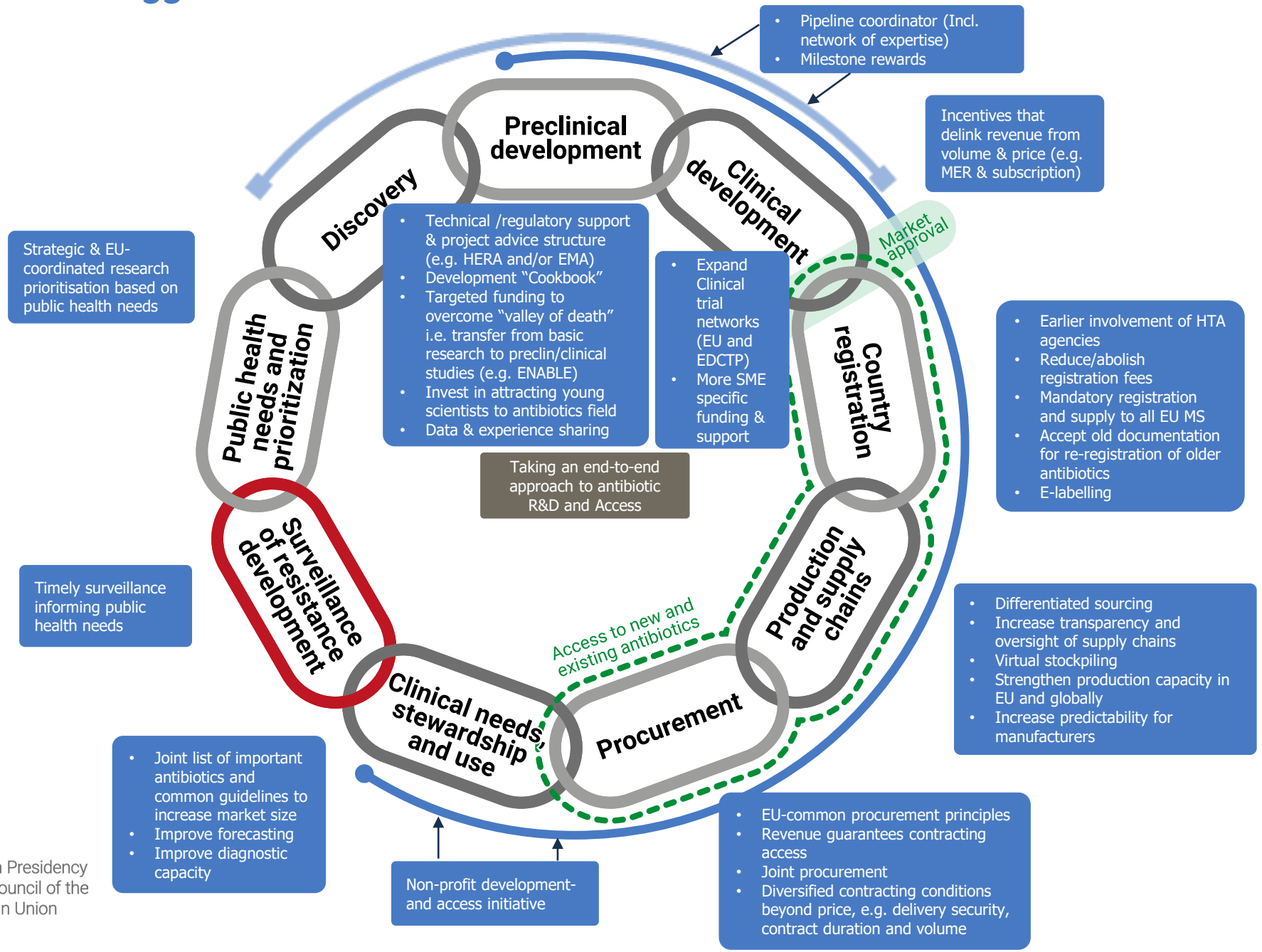
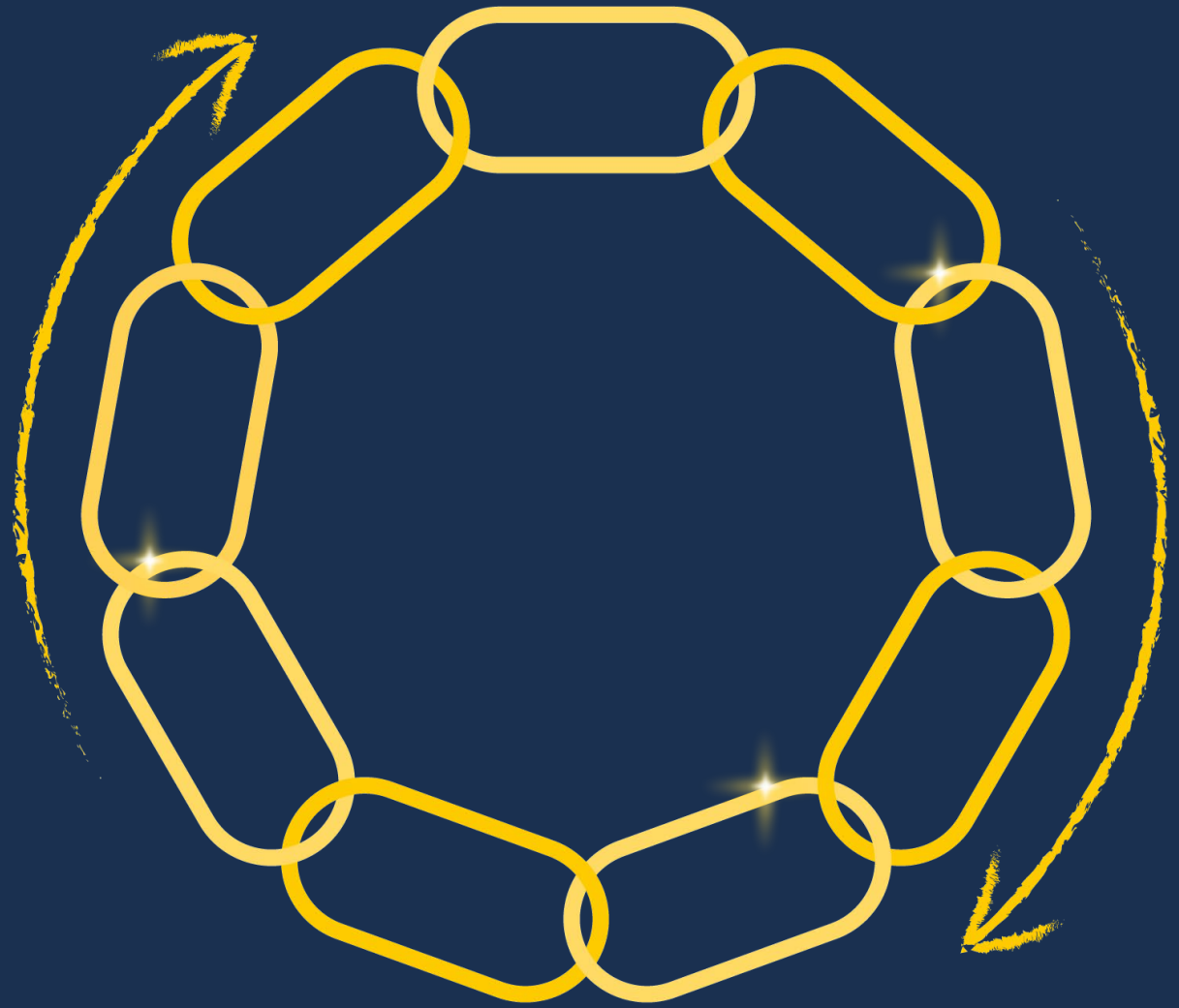
Suggested solutions to connect the links in the chain



The golden chain of antibiotic Research & Development and Access



Additional background on key terms and challenges

- **End-to-end approach:** an approach that, in order to achieve s*ustainable access to effective antibiotics*, considers how the entire chain of actors, investments, and regulatory measures implicated in developing and bringing novel and existing antibiotics to patients, should work to achieve this goal.

- **Additional research prioritisation tools needed:** The WHO has developed a global list of 12 priority pathogens for which new treatments are needed (3 critical, 6 high, 3 medium). The list is developed to help guide funders and researchers in ensuring that the work they undertake is targeting priority public health needs. Additionally, four *Target Product Profiles* (TPPs) have been developed by the WHO (addressing enteric fever, gonorrhea, neonatal sepsis and urinary tract infections) to provide further detailed guidance for the research and development community. Regional priority lists would be a useful complement and additional TPPs would be beneficial.

- **Lack of research coordination and prioritisation by funders:** Funders of R&D are currently not coordinating their efforts and funding priorities enough. It is currently only possible to get a good overview of what is being funded and how it relates to public health needs through the retrospective pipeline analysis carried out by WHO every 2nd year. In 2021, only 27 out of 45 antibiotics in clinical development (60%) were targeting WHO bacterial priority pathogens. Just two of six new compounds identified as innovative were active against at least one multidrug-resistant Gram-negative bacterium from the "critical" category of the Priority Pathogens List.

- **Projects start without clear clinical or public health relevance**: Often early research projects are defined based on other considerations and interests and fail to consider clinical needs and wider public health relevance. Funders do not necessarily require this type of consideration in calls for proposals or when giving out grants

- **Unresolved scientific challenges:** It has previously been estimated that traditional anti-bacterial drugs have a ten-fold lower yield in the discovery stage of identifying promising new compounds when compared to all other drug classes. Many of the scientific challenges leading to these higher failure rates, such as penetration issues, efflux, and managing toxicity, remain unresolved, and likely still affect any traditional antibiotic compounds under development today. The underfunding of research into these key issues, pushes these problems downstream only to be exposed at later and far more expensive stages of development.

- **Lack of sustainable, long-term and targeted funding:** Limited and unpredictable funding has a discouraging effect on early stages of research and development. Short-term project-funding also risk expertise, equipment and staff being lost when funding ends prematurely. Often time is spent on writing applications to secure additional funding to sustain the research project. Lack of targeted funding means researchers often struggle crossing the so-called "valley of death" (moving a compound from basic to clinical research) because public funding for this phase is limited, and securing private venture capital is almost impossible without an indication that larger companies will eventually acquire the compound.

- **Lack of access to expert advice**: very few structures exist to provide guidance and support for researchers and SMEs trying to advance a promising compounds. Confidentiality of data may also be a barrier to seeks external advice. Structures like ENABLE (originally set up by the EU's Innovative Medicines Initiative) was set up with the purpose to building up a structure where researchers can share their research results and get technical support. ENABLE has been supported by the Swedish Government to make sure the structure didn't disappear when EU project funding ended but remains limited in size and capacity.

- **Lack of expertise on how to scale up a project to proof of concept**: academic research teams do not necessarily sit on the expertise on how to advance promising compounds to proof of concept in pre-clinical testing. Public funding available for this kind of work is also scarce.

- **Lack of research coordination**: lack of coordination of antibiotic R&D, including of priority setting, clinical trials and research funding leads to siloed efforts and can hinder research progress by allowing the same mistakes to be repeated. In particular when knowledge and data sharing isn't mandated.

- **Lack of knowledge sharing (e.g., failures)** Lack of collaborative approaches and data sharing can impede progress and cause wasteful duplication of research efforts in particular when results from research failures are not shared/published.

- **Challenging recruitment of patients (time & costs)** Recruitment of suitable patients for trial participation is challenging and expensive. Bacterial infections progress rapidly; therefore, potential trial participants need to be enrolled quickly into a trial, often before a precise diagnosis can confirm the suitability of the patients. Moreover, as these patients cannot be moved between hospitals if infected with multidrug-resistant pathogens, many hospitals and doctors, sufficiently trained in the trial protocol, need to be recruited and involved.

- **Non-inferiority trials (lower prices vs competing products):** trials that show that a new antibiotic is not inferior to existing treatment options are typically the only clinical trial set up possible with small patient cohorts. When new antibiotics are approved based on non-inferiority trials it is difficult to make the case for higher payments than existing available treatments (also see point about HTAs).

- **Lack of information on development costs**: the actual costs of clinical trials and drug development are not publicly available. Companies consider this data to be commercially confidential. Lack of transparency about the costs associated with antibiotic R&D makes informed discussions about the size of new financial incentives difficult.

- **Insufficient capacity in SMEs**: academic researchers and SME's do not necessarily sit on actual drug development experience and knowledge. In 2020 the Pew Trust estimated that 70% of the small companies involved in early antibiotic R&D have no previous experience with bringing a product all the way to the market.

- **Risk of bankruptcy despite successful approval (SMEs);** A few smaller companies, such as Achaogen and Melinta Pharmaceuticals, have in recent years succeeded in shepherding early-stage discoveries through clinical development and brought new antibiotics to market. Yet over a twelve-month period in 2019 and 2020, both companies filed for bankruptcy as the near-term revenues for each company's new antibiotics were not sufficient to sustain their businesses.

- **Selective registration in most profitable markets:** Registration of new antibiotics in smaller or poorer countries is often delayed. Of the novel antibiotics entering the global pharmaceutical market between 1999 and 2014, only 12 out of 21 products were registered in more than 10 countries. For antibiotics introduced since 2014, registrations have been filed in fewer than five countries per year, slowing down approval and use.

Continuation – Additional background on key terms and challenges

- **Uncertain and volume dependent revenues (at odds with stewardship efforts)** When new antibiotics come to market, they are not necessarily becoming first line treatment option. In fact, often newer drugs are used sparingly to ensure resistance doesn't develop too quickly. Sales volumes are therefore not appropriate tool for generating revenue. Delinked financial incentives such as milestone rewards, subscription models and market entry rewards etc. have instead been proposed as a way to finance antibiotic R&D.

- **Lack of funding available for distribution and post-approval studies**: public financing available for studies to improve clinical use of the new drugs is scarce. These studies are different from the studies that are required to receive market authorisation but are still important from a public health perspective (such studies could be optimisation studies that for example test dosage and combinations of drugs to avoid/delay resistance development).

- **The value of new antibiotics is not fully reflected in HTA:** Health technology assessment (HTA) methods do not currently assess the multiple values of new antibiotics, which may be non-inferior to existing ones and hence hard to motivate to be paid more on this performance indicator, but are still valuable because they e.g., help reduce usage pressure on other antibiotics (variety value) or can be kept in reserve for future usage (insurance value).

- **Fragile supply chain with overreliance on few producers & countries**: Current global supply chains are fragile and rely on just a few manufacturers based in a few countries. For some antibiotics, there are just one or two major manufacturers of the active pharmaceutical ingredient (API) supplying global production; therefore, disruptions can lead to global stockouts and shortages.

- **Low profit margins**: very low profit margins and short-term contracts in public procurement of off-patent antibiotics may benefit consumers with low prices, but can fuel aggressive competition between generic companies, which risks putting production standards and sustainability of the supply chain at risk

- **Environmental pollution from production:** Antibiotic discharge from manufacturing facilities is a result of inadequate production standards and waste removal at sites for raw materials, API manufacturing and antibiotics production. Such discharge is a driver of resistance development in the environment. Additional environmental rules for antibiotic procurement to improve transparency and discourage improper practices throughout the supply chain has been tested in some countries. WHO has also explored how rules on Good Manufacturing Practice (GMP) could be amended to include environmental obligations.

- **Lack of supply chain transparency**: A lack of transparency in the global supply chains makes it difficult to assess the full extent of the current system's fragility and mitigate the risks.

- **Short-term contracting, price pressure, rigid procurement regulation:** public procurement relies on short-term contracts which do not foster long-term relationships with suppliers, which in most industries is a key tool to build well-coordinated supply chains across several organizations; moreover, public procurement has problems in recognizing other value-creating elements in suppliers' offerings beyond low prices, which are in turn often associated with poor/fragile supply systems upstream.

- **Fragmented and/or decentralised purchasing:** often purchasing of medicines including antibiotics are done at regional/county level in countries creating a complex procurement landscape with many small, irregular markets with low predictability for antibiotic suppliers to supply.

- **Lack of purchasing competence:** public purchasing organizations do not necessarily have the expertise and insight into what products and services that are most needed clinically and what is beneficial from a public health perspective. They are often also mandated to use strictly measurable indicators of value (e.g., low price).

- **Locally diverging treatment guidelines in EU:** Every single country, even with similar resistance levels and patterns, tend to have different preferred antibiotics (including dosages and formulations) for exactly the same indication and patient type. This practice reduces the market size for a particular antibiotic (even at the level of packaging) and makes it less economically attractive for suppliers to provide for the long term.

- **Use also guided by availability**: antibiotics use may in some cases be guided by what is available in a certain country rather than what the optimal treatment option is (see also points on treatment guidelines).

- **Unclear overview of needs/demands**: single countries often have opaque and unconnected IT and journal systems making it difficult to identify which antibiotics are currently used. Regional/county level disconnected systems make it hard to aggregate demand at national levels. In turn, this means antibiotic suppliers have little overview of current and especially future needs and demands for a specific country (and region).

- **Lack of common lists of prioritized antibiotics:** due to the fragmented public procurement landscape, unconnected IT systems etc. it is difficult to identify prioritised antibiotics and aggregate regional demand within the EU (see point on "Unclear overview of needs/demands").

- **Lack of (transnational) guidance for introducing new antibiotics:** There is currently no guidance available to support countries introducing new antibiotics into companies/suppliers. This is of particular concern in countries with weaker health systems.

- **Limited global surveillance:** Surveillance and capacity for monitoring resistance development is weak and uneven, particularly in low and middle-income countries. The 2022 report from WHO's Global antimicrobial resistance surveillance system noted a low surveillance coverage in most countries providing data to the new global system, which raises concerns about data representativeness. Less than one-half of countries (48.6%) have all their reporting laboratories enrolled in external quality assessment, which might affect data quality.