Europeiske tiltak for å sikre tilgang til antibiotika, nye og gamle

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Antibiotikaresistens symbol

Norwegian Business School

MIA - Measures for
Improved **A**vailability
of medicines project

Norwegian Institute of Public Health

Mangler nye, effektive antibiotika

"The current clinical pipeline is **dominated by derivatives of established antibiotic classes**…

Although **incremental improvements** in susceptibility rates among derivatives benefit patients in advanced health care systems within specific geographical regions, these concepts are **not adequate for carbapenem-resistant strains** of *Enterobacterales* (especially *Klebsiella* and *Escherichia coli*), *Acinetobacter*, and *Pseudomonas*…

An **initial glimpse of progress** is evident as innovative agents progressed to **Phase 1 clinical trials**. However, **an influx of more agents advancing to clinical development is essential given the inherent risks associated with novel chemistry and targets**."

Theuretzbacher, Oct 2023, Evaluating the innovative potential of the global antibacterial pipeline, Clinical Microbiology and Infection.

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"Innovative" antibiotika mot "kritiske" Gram-negative patogen i klinisk forsøk

Type	Company size	Clinical Trial Phase	Innovative	CRE	CRAB	CRPA
Antibacterial agent	Large	3	Yes	Yes		
Antibacterial agent	Small	1	Yes	Yes	Maybe	Maybe
Antibacterial agent	Large	1	Yes	Yes		
Peptide	Large	1	Yes		Yes	
Peptide	Small	1	Yes		Yes	

Tre **små** selskaper som utvikler **innovative** antibiotika mot **høy eller medium** patogen.

Theuretzbacher, Oct 2023, Evaluating the innovative potential of the global antibacterial pipeline, Clinical Microbiology and Infection.

Preklinisk pipeline er sterkere

- "The preclinical pipeline is **dynamic** and **innovative**, with agents being developed in many parts of the world to prevent and treat drug-resistant bacterial infections."
- N=217 kandidater
- 1/3 stanses hvert år

- CARB-X har støttet **92 FoU-prosjekter** i 12 land, alle fokusert på WHOs prioriterte patogen
- 61 (66%) av 92 er antibakterielle midler, inklusiv 23 (**38%** av 61) ikke-tradisjonell

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Nye antibiotika er utilgjengelige

Approval and commercial launch in fourteen high-income countries of NME antibacterials first approved by FDA, EMA, PMDA, or Health Canada, 2010-2019

INN	1st Approval	US	EMA*	UK	Sweden	France	Germany	Italy	Norway	Spain	Greece	Romania	Croatia	Denmark	Japan	Canada	Launches
cefiderocol	14-Nov-19	102	161	306	413												3
lascufloxacin	20-Sep-19														103		1
lefamulin	19-Aug-19	21	343														1
imipenem-cilastatin/ relabactam	16-Jul-19	321	212	382	382				290								4
omadacycline	2-Oct-18	122															1
sarecycline	1-Oct-18	92															1
eravacycline	27-Aug-18	35	24														1
plazomicin	25-Jun-18	6															1
meropenem/ vaborbactam	29-Aug-17	33	448	815	1037	1064											4
delafloxacin	19-Jun-17	196	910	1121													2
bezlotoxumab	21-Oct-16	115	89	174	131	1045	527	618	206	557					413		9
ceftazidime/ avibactam	25-Feb-15	35	484	748	827	1967	720	1049	310	999	980	933	1184	841			12
ceftolozane/ tazobactam	14-Dec-14	49	278	352	383	598	322	657	383	443	383	808	657	352	1630	291	14
oritavancin	6-Aug-14	56	224														1
tedizolid	20-Jun-14	10	276	315	438	577	276	1046	390	294	681	742		276	1432		12
dalbavancin	23-May-14	39	272	914	1279	1097	918	740		619	954	862	923				10
fidaxomicin	27-May-11	35	192	371	371	542	585	889	385	554	432	797	1711	371	2651	1648	14
ceftaroline	29-Oct-10	64	663	726	764	844	717	1007	755	1162	1315	795	2764	734			12
N approved or launched	18	17	14	11	10	8	7	7	7	7	6	6	5	5	5	2	0

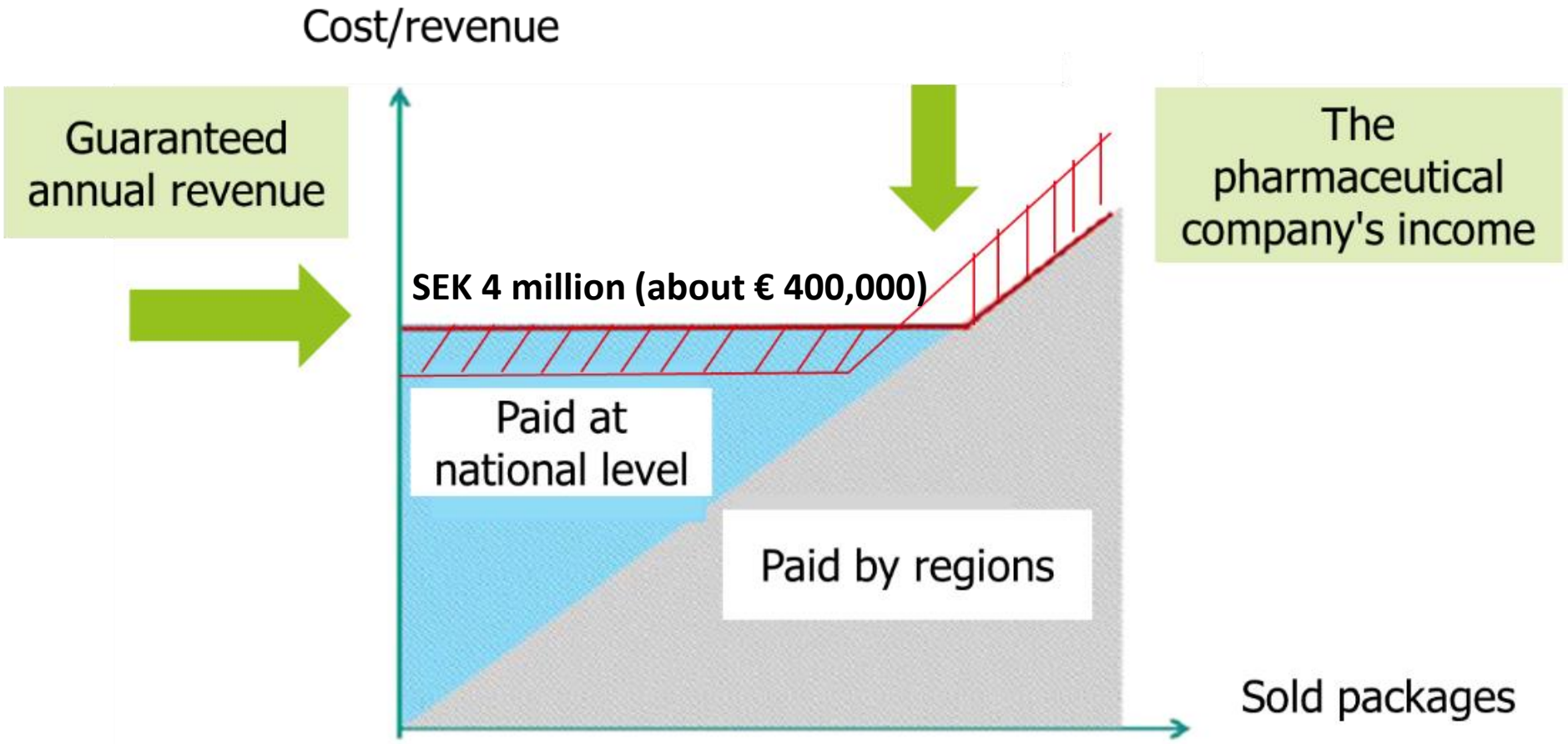
All data as of 12/31/20

Notes: INN = international nonproprietary name; Empty cell = not commercially launched, except in the EMA column where empty cell = not approved by EMA; Number = lag from first approval to commercial launch, in days, except in the EMA column where number = lag from first approval to EMA approval, in days. The US was the country for all first approvals and first commercial launches, with the exception of lascufloxacin, approved and launched only in Japan. Color key: green = lowest lag in days; red = highest lag in days; yellow = 50th percentile lag in days.

WHO essential medicine

Source: Outterson K, Orubu ESF, Rex J, Årdal C, Zaman MH. Clin Infect Dis 2021.

Sveriges inntektsgaranti



- MSD - ceftolozan-tazobactam
- MSD - imipenem-cilastatin-relebactam
- Shionogi - cefiderocol
- Pharmaprim - meropenem-vaborbactam
- Unimedic Pharma - fosfomycin

Sources: Questions and answers about procurement in pilot study for new remuneration model. Public Health Agency of Sweden: https://www.folkhalsomyndigheten.se/contentassets/92ec9ceb2f2f428cb683add24b4f785b/faq-upphandling-pilotstudie.pdf

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Potential European annual revenue guarantee

EC / EMA

Marketing authorization holder

Commit to access & stewardship reqs

Opt in

New antibiotics matching public health needs

List of eligible antibiotics

European Commission

Joint tender description for revenue guarantee

Signed contracts for revenue guarantees

Guarantee payment

Normal national procurement and reimbursement processes

Guarantee amount owed

National governments

Opt in (a set minimum number)

Important antibiotics with vulnerable supply

Sources: Årdal, Lacotte, Edwards, Ploy. 2021, https://doi.org/10.3390/antibiotics10060749
Slovenian Presidency, https://www.jazmp.si/en/slovenian-presidency-of-the-council-of-the-eu-2021/

Hvorfor en inntektsgaranti?

1. Den sikrer **tilgang** til de utvalgte antibiotikaene, samtidig som nasjonale prosesser som HTA-, pris- og innkjøpsmodeller går som **vanlige**.

   "11 of 13 countries would prefer a common, multinational incentive, so long as it is independent from national medicine pricing, procurement, and reimbursement processes."

2. Det belønner **suksess**.

   Fire nye antibiotika har fått markedsføringstillatelse og blitt lagt til WHOs «Essential Medicines List» i det siste tiår, samtidig har 10+ blitt stanset i klinisk utvikling. Utviklingen av innovative antibakterielle midler svikter mer ofte pga vitenskapelige årsaker.

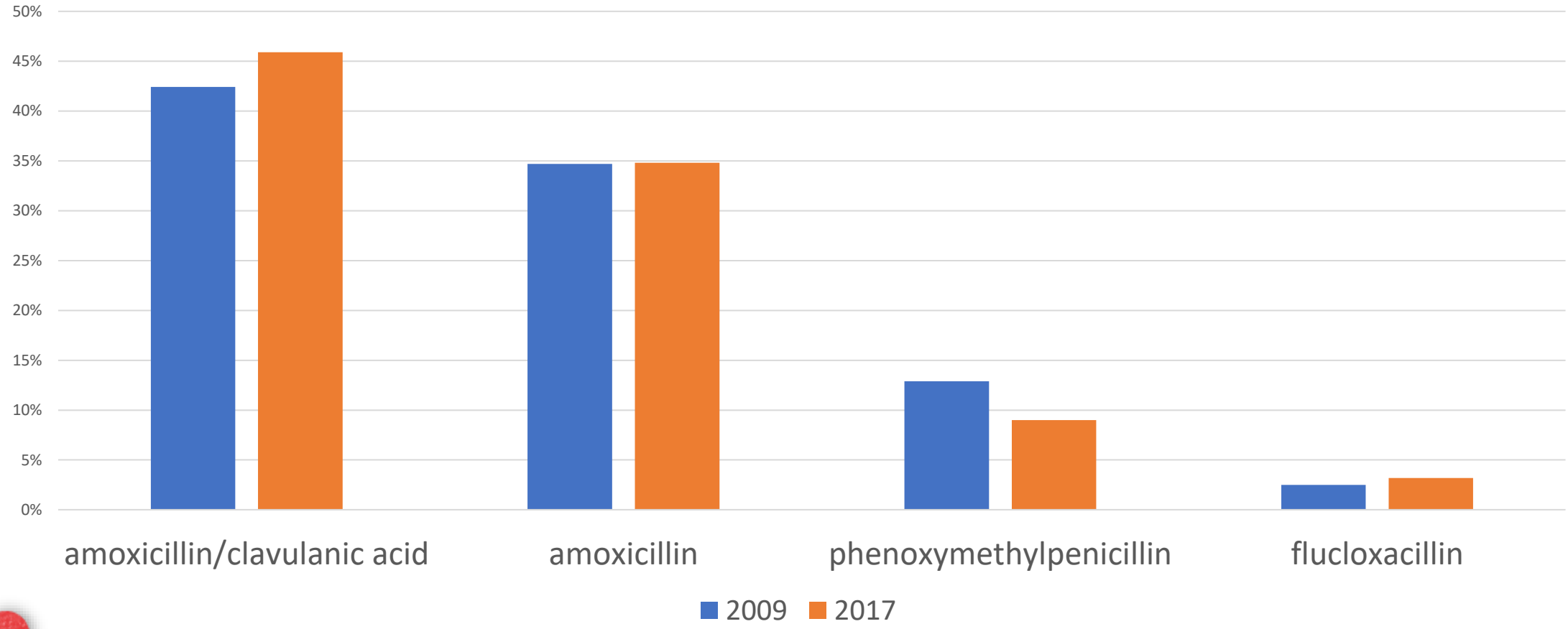
3. Det kan sikre **lønnsomhet** for innovatører og leverandører av både **generiske og nye** antibiotika.

   Inntektsgarantibeløpet er fleksibelt, skreddersydd til antibiotikumets egenskaper.

Sources: Årdal, Lacotte, Edwards, Ploy. 2021, https://doi.org/10.3390/antibiotics10060749
Pew Trusts, 2019. https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2019/five-year-analysis-shows-continued-deficiencies-in-antibiotic-development

Løsninger trengs for elder antibiotika

Penicillin consumption (DDDs) in the community 30 EU/EEA countries; percentage of total penicillin consumption



Bruyndonckx et al. J Antimicrob Chemother (2021).

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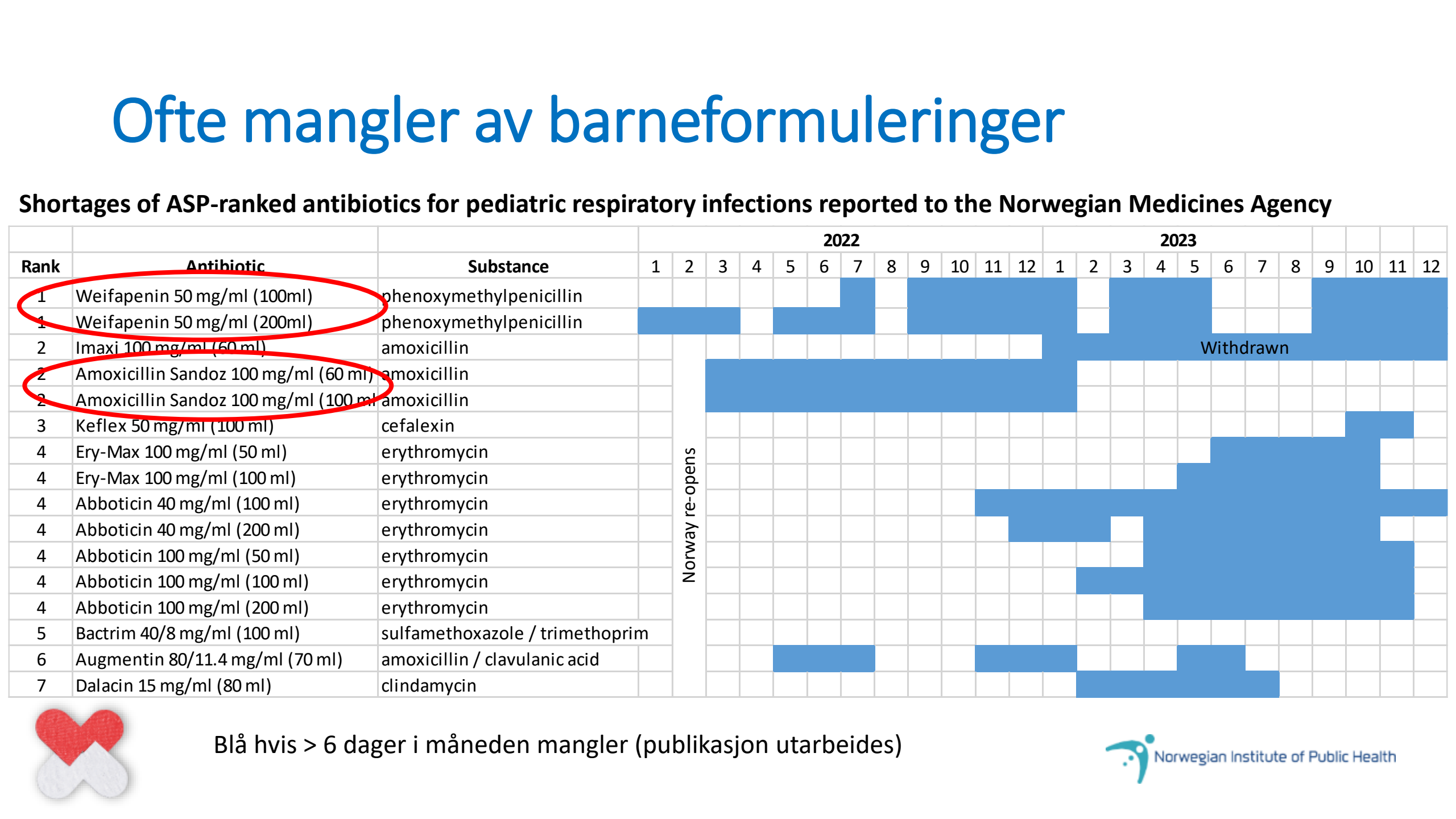
Ofte mangler av barneformuleringer

Shortages of ASP-ranked antibiotics for pediatric respiratory infections reported to the Norwegian Medicines Agency

Rank	Antibiotic	Substance
1	Weifapenin 50 mg/ml (100ml)	phenoxymethylpenicillin
1	Weifapenin 50 mg/ml (200ml)	phenoxymethylpenicillin
2	Imaxi 100 mg/ml (60 ml)	amoxicillin
2	Amoxicillin Sandoz 100 mg/ml (60 ml)	amoxicillin
2	Amoxicillin Sandoz 100 mg/ml (100 ml)	amoxicillin
3	Keflex 50 mg/ml (100 ml)	cefalexin
4	Ery-Max 100 mg/ml (50 ml)	erythromycin
4	Ery-Max 100 mg/ml (100 ml)	erythromycin
4	Abboticin 40 mg/ml (100 ml)	erythromycin
4	Abboticin 40 mg/ml (200 ml)	erythromycin
4	Abboticin 100 mg/ml (50 ml)	erythromycin
4	Abboticin 100 mg/ml (100 ml)	erythromycin
4	Abboticin 100 mg/ml (200 ml)	erythromycin
5	Bactrim 40/8 mg/ml (100 ml)	sulfamethoxazole / trimethoprim
6	Augmentin 80/11.4 mg/ml (70 ml)	amoxicillin / clavulanic acid
7	Dalacin 15 mg/ml (80 ml)	clindamycin



Blå hvis > 6 dager i måneden mangler (publikasjon utarbeides)

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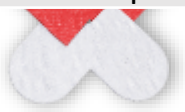
Komparativ tilgjengelighet (# MAHs) barneformuleringer klassifisert som kritiske og sårbare av Sverige

Antibiotic	Spectrum	DEN	FIN	NED	NOR	SWE
Amoxicillin 50 mg/ml oral suspension	Broad	2	1	5	0	2
Amoxicillin 100 mg/ml oral suspension	Broad	0	2	2	2	4
Amoxicillin/clavulanic acid 50 mg/ml + 13 mg/ml oral suspension	Broad	3	1	2	0	1
Azithromycin 250 mg tablet	Broad	5	4	8	0	6
Ceftibuten 36 mg/ml oral suspension	Broad	0	0	0	0	0
Cefadroxil 100 mg/ml oral suspension	Broad	0	0	0	0	2
Cefixime 20 mg/ml oral suspension	Broad	0	0	0	0	0
Ciprofloxacin 100 mg/ml oral suspension	Broad	0	0	3	0	4
Clindamycin 15 mg/ml oral suspension	Narrow	0	1	1	1	1
Erythromycin 100 mg/ml oral suspension	Broad	1	0	0	2	1
Flucloxacillin 50 mg/ml oral suspension	Narrow	0	0	0	0	1
Flucloxacillin 125 mg tablet	Narrow	0	0	0	0	1
Metronidazole 40 mg/ml oral suspension	Broad	1	0	1	1	1
Phenoxymethylpenicillin 50 mg/ml oral suspension	Narrow	3	1	0	1	3
Phenoxymethylpenicillin 250 mg tablet	Narrow	0	0	3	0	1
Sulfamethoxazole/trimethoprim 40 mg/ml + 8 mg/ml oral suspension	Broad	0	0	1	1	2
Trimethoprim 10 mg/ml oral suspension	Broad	1	1	0	1	1



(Publikasjon under vurdering)

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Cefadroxil 100 mg/ml oral suspension	Broad	0	0	0	0	2
Cefixime 20 mg/ml oral suspension	Broad	0	0	0	0	0
Ciprofloxacin 100 mg/ml oral suspension	Broad	0	0	3	0	4
Clindamycin 15 mg/ml oral suspension	Narrow	0	1	1	1	1
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Trimethoprim 10 mg/ml oral suspension	Broad	1	1	0	1	1

(Publikasjon under vurdering)

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Sykehusinnkjøp leder veien

Denmark, Iceland, and Norway – pooled hospital tenders

Criteria	Weight
Price	25%
User preferences	30%
Surety of supply	15%
Environment	30%

Transparens – viktig

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EU-JAMRAI-2 (oppstart jan 2024)

Hvert land vil identifisere en håndfull høyprioriterte antibiotika, for eksempel smalspektrede antibiotika og barneformuleringer

9.2 – Etterspørsel

- Nasjonale etterspørselsbarrierer
- Identifiser potensielle målrettede intervensjoner
- Begynn å implementere målrettede intervensjoner og dokumenter

9.3 – Forsyning

- Identifiser potensielle inngrep på tilbudssiden (som standardisering av styrker, pakkestørrelser og enhetsdispensering samt brosjyrer) for å forbedre tilgjengeligheten
- Arbeid med EMA og nasjonale medisinmyndigheter for å undersøke potensielle intervensjoner, som gjensidig anerkjennelse av utvalgte antibiotika samt kjøp av gamle og utløpte dokumenter
- Start implementering (samarbeid, hvis det er aktuelt) og dokumenter

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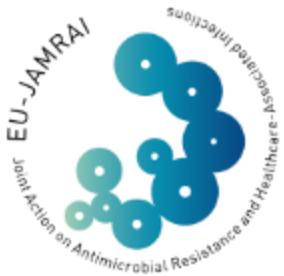
Tusen takk! Spørsmål?



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