



Joint Action
Antimicrobial Resistance and
Healthcare-Associated Infections



Co-funded by the
Health Programme
of the European Union

Do we need new financial models to secure supply of old antibiotics?

Work Package 9, Research & innovation
WP Leaders: Marie-Cécile Ploy and Christine Årdal
Date: September 6, 2018
Author: Dr. Christine Årdal, chaa@fhi.no



Norwegian Institute of Public Health

“Forgotten” antibiotics



Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag



Short Communication

Forgotten antibiotics: a follow-up inventory study in Europe, the USA, Canada and Australia [☆]



Céline Pulcini ^{a,*}, Simone Mohrs ^b, Bojana Beovic ^c, Inge Gyssens ^{d,e}, Ursula Theuretzbacher ^f, Otto Cars ^b on behalf of the ESCMID Study Group for Antibiotic Policies (ESGAP), ReAct Working Group on Old Antibiotics ¹

^a Service des maladies infectieuses exotiques, Université de Lorraine Faculté de médecine, Centre hospitalier régional universitaire (CHRU) de Nancy, Nancy, France

^b ReAct—Action on Antibiotic Resistance, De

^c University Medical Centre Ljubljana, Ljubljana

^d Department of Medicine, Radboud University

Corisius-Williamina Hospital, Nijmegen, The Netherlands

^e Hasselt University, Hasselt, Belgium

^f Center for Anti-Infective Agents, Vienna, Austria

ARTICLE INFO

Article history:

Received 1 August 2016

Accepted 19 September 2016

Keywords:

Bacterial resistance

Drug approval

Drug marketing

Antibiotic stewardship

36 selected antibiotics, including:

- Benzylpenicillin (penicillin G)
- Benzathine benzylpenicillin
- Procaine benzylpenicillin
- Phenoxymethylpenicillin (penicillin V)

The examples are all “key access antibiotics” according to WHO EML (20th ed.).

“Forgotten” antibiotics



Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag



Short Communication

Forgotten antibiotics: a follow-up inventory study in Europe, the USA, Canada and Australia [☆]



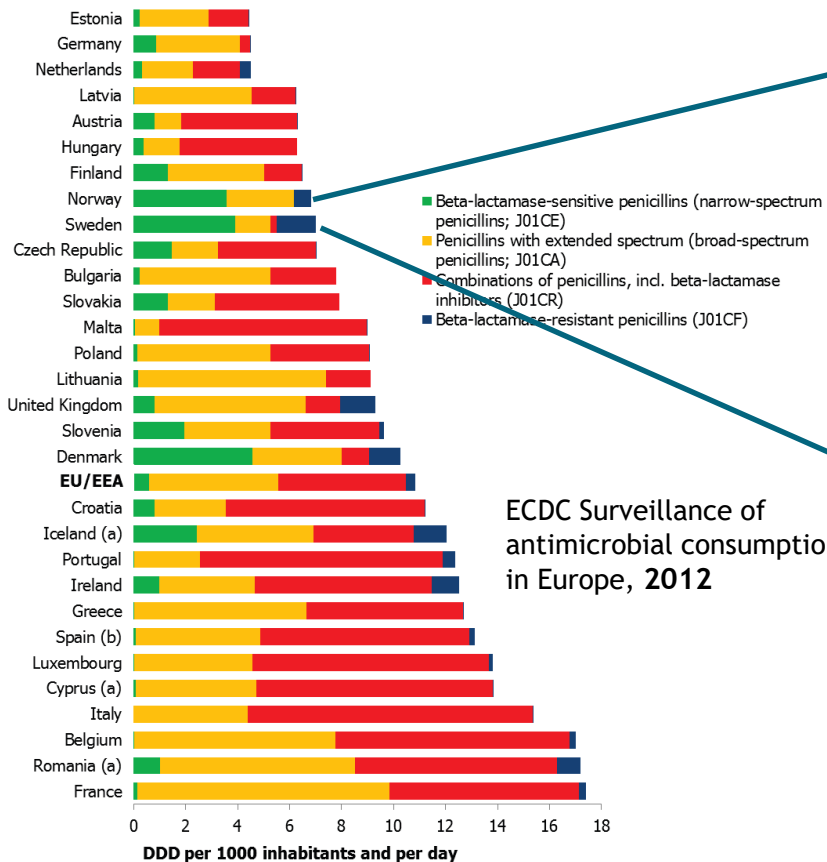
Céline Pulcini ^{a*}, Simone Mohrs ^b, Bojana Beovic ^c, Inge Gyssens ^{d,e},
Ursula Theuretzbacher ^f, Otto Cars ^b on behalf of the ESCMID Study Group for Antibiotic
Policies (ESGAP), ReAct Working Group on Old Antibiotics ¹

“In conclusion, despite the ongoing bacterial resistance crisis, the situation regarding the availability of ‘forgotten antibiotics’ has worsened since 2011.”

in 13 countries and decreased in 17. In conclusion, despite the ongoing bacterial resistance crisis, the situation regarding the availability of ‘forgotten antibiotics’ has worsened since 2011. Urgent measures are needed to ensure better availability of these antibiotics on a global scale as a conservation measure to ensure sustainable and responsible use of antibiotics.

© 2016 Elsevier B.V. and International Society of Chemotherapy. All rights reserved.

Consumption of penicillins in Europe



In Norway in 2016, the proportion of narrow-spectrum penicillins of total sales was **26%** of overall sales. (NORM/NORM-Vet)

In Sweden in 2017, the proportion of narrow-spectrum penicillins used in outpatient care was **41%**. (Swedres/Svarm)

Select penicillins - MA holders



Number of marketing authorization holders for human consumption

Antibiotic	Norway	Sweden	Uganda	USA
Benzylpenicillin (penicillin G)	2	2	6	5
Benzathine benzylpenicillin	0	0	2	1
Procaine benzylpenicillin	0	0	1	1
Phenoxymethylpenicillin (penicillin V)	2	4	5	5

Preliminary findings based upon Norwegian Medicines Agency, Swedish Medical Products Agency, Ugandan National Drug Authority, Drugs@FDA

Why they are “fragile”...



Approximate number of active pharmaceutical ingredient producers

API	EDQM Certification*
Benzylpenicillin sodium	1 - Sandoz
Benzylpenicillin potassium	2 - Sandoz, Fersinsa
Benzylpenicillin procaine	1 - Sandoz
Benzylpenicillin (benzathine) tetrahydrate	1 - Sandoz
Phenoxymethylpenicillin potassium	2 - Sandoz, Biotika
Amoxicillin trihydrate	13

*Verifies the compliance of pharmaceutical substances with European Pharmacopoeia standards;
https://extranet.edqm.eu/publications/recherches_CEP.shtml

Removal of EDQM certification



Substance Number	Substance	Certificate Holder	Certificate Number	Issue Date	Status	End date	Type
149	Phenoxymethylpenicillin potassium	DSM Anti-Infectives B.V. NL 2613 AX Delft	R1-CEP 1994-017-Rev 01	16/04/2002	WITHDRAWN BY HOLDER	26/04/2005	Chemistry
149	Phenoxymethylpenicillin potassium	Biotika A.S. SK 97613 Slovenska Lupca	R1-CEP 1997-043-Rev 02	08/02/2008	VALID		Chemistry
149	Phenoxymethylpenicillin potassium	North China Pharmaceutical Co., LTD. CN 050 015 Shijiazhuang	R0-CEP 2006-019-Rev 00	26/11/2008	WITHDRAWN BY EDQM	04/11/2013	Chemistry
149	Phenoxymethylpenicillin potassium Material Code Numbers 450401, 450402 and 451786	SANDOZ GMBH AT 6250 Kundl	R2-CEP 1994-012-Rev 06	15/05/2017	VALID		Chemistry

European Pharmacopoeia standards; https://extranet.edqm.eu/publications/recherches_CEP.shtml

Select penicillins - max Norwegian sales price



Maximum sales price per package in Norway

Antibiotic	Strength/Pack size	Max sales price
Benzylpenicillin (penicillin G)	600mg, powder for injection (n=10)	€ 12
Phenoxymethylpenicillin (penicillin V)	50 mg/ml mixture, (200 ml)	€ 14
Ampicillin	1 g solution (n=1)	€ 5

Norwegian Medicines Agency (prices in NOK, €1 = 9.7 NOK)

Example of ampicillin



- Ampicillin is a “key access” antibiotic as defined in WHO EML.
- It is the first choice for community acquired pneumonia (severe), complicated severe acute malnutrition, and sepsis in neonates and children.
- Norway currently has no marketing authorization holder for ampicillin. BMS decided to give up its license as of March 2018.
- Yet, it appears that other countries still have access to ampicillin.

Impact of shortages and non-supply



Shortages, stockouts and scarcity

The issues facing the security of antibiotic supply and the role for pharmaceutical companies

WHITE PAPER

31 MAY 2018

WHAT IS THE ISSUE?

WHAT ARE PHARMACEUTICAL COMPANIES

“Supply chain collapse leads to antibiotic shortages, which are linked to disease outbreaks and antimicrobial resistance.”

Authors
Deirdre Cogan
Kantar Kantar
Japanese K. Iyer

Access to Medicine Foundation
NanLing 2018
1043 CG Amsterdam
The Netherlands

E ijer@access-to-medicine-foundation.org
T +31 (0)20 475 35 35
W www.access-to-medicine-foundation.org

ACCESS TO
MEDICINE
FOUNDATION

Impact of shortages and non-supply



RESEARCH ARTICLE

Shortages of benzathine penicillin for prevention of mother-to-child transmission of syphilis: An evaluation from multi-country surveys and stakeholder interviews

“Congenital syphilis remains a significant contributor to early infant mortality, particularly in low- and middle-income countries. There are several reasons for this, but one of the most important is a global shortage of [benzathine penicillin G].”

stakeholder interviews. PLOS Med 14(12): e1002473. <https://doi.org/10.1371/journal.pmed.1002473>

Academic Editor: Nicola Low, University of Bern, SWITZERLAND

Background

Benzathine penicillin G (BPG) is the only recommended treatment to prevent mother-to-child transmission of syphilis. Due to recent reports of country-level shortages of BPG, an evaluation was undertaken to quantify countries that have experienced shortages in the past 2 years and to describe factors contributing to these shortages.

New business models needed?



Market is fragile with low returns and increasingly diminishing size.

For example, “the proportion of narrow-spectrum penicillins of total sales (in Norway) was **32%** of overall sales in year **2000** and has decreased to **26%** in **2016.**”
NORM/NORM-Vet

New business models needed?



Market is fragile with low returns and increasingly diminishing size.

Sandoz 2017 net sales by franchise

(in USD millions and % growth in constant currencies)

RETAIL GENERICS 8 409 / - 3%

84%

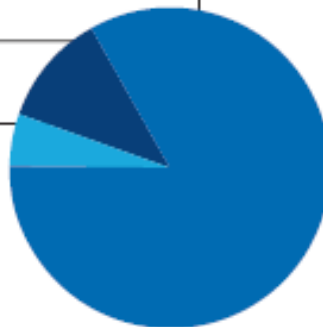
BIOPHARMACEUTICALS 1 135 / 12%

11%

ANTI-INFECTIVES 516 / - 2%

(partner label/API)

5%



TOTAL 10 060 / - 2%

Proposals for improving the market



Availability of antibiotics

Reporting of Government commission

In 2017 there were 91 prescriptions per 1000 people for narrow-spectrum penicillins, i.e., less than one million prescriptions per year.
(Swedres/Svarm)

“An analysis...shows that there is a relationship between the risk of a product disappearing and a low sales value..Therefore, [The Swedish Dental and Pharmaceutical Benefits Agency] will consider this aspect for applications on price increases for such antibiotics which the Public Health Agency of Sweden has assessed are of special medical value.”

Proposals for improving the market



DRIVE-AB REPORT

Revitalizing the antibiotic pipeline

Stimulating innovation while driving sustainable use and global access

“We also recommend a long-term supply continuity model designed to ensure continued supply of potentially low-volume but critical generic antibiotics through a series of annual fixed payments to the supplier.”

Maybe the market is improving slightly?



MINI REVIEW

10.1111/j.1469-0691.2009.02726.x

Impact of pneumococcal conjugate vaccine on infections caused by antibiotic-resistant *Streptococcus pneumoniae*

R. Dagan

Pediatric Infectious Disease Unit, Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Abstract

“Vaccines can reduce pneumococcal resistance in vaccinated and unvaccinated populations by reducing the carriage of antibiotic-resistant serotypes...”

disease (IPD) in children and the elderly. An increase in IPD rates caused by antibiotic-resistant serotype 19A isolates can also occur without vaccination; reports indicate increases in regions characterized by extensive antibiotic use, underscoring the importance of strategies to contain antibiotic resistance.

Efforts to assess and take action



- World Health Organization is initiating an assessment of manufacturing capacity and other market characteristics for selected antibiotics facing shortages risks.
- The European Union Joint Action on Antimicrobial Resistance (AMR) and Healthcare-Associated Infections (HCAI) is exploring and detailing European strategies to implement mechanisms to increase innovation and other means to fight against AMR and HCAI.

Mission of the EU-JAMRAI



EU-JAMRAI is a European Union Joint Action on Antimicrobial Resistance (AMR) and Healthcare-Associated Infections (HCAI) that brings together 44 partners from 28 countries and more than 30 stakeholders. Our mission is to **foster synergies** among EU Member States by **developing and implementing effective *One Health* policies** to fight the rising threat of AMR and to reduce HCAI.

Thank you!

EU-JAMRAI



Joint Action
Antimicrobial Resistance and
Healthcare-Associated Infections



Co-funded by the
Health Programme
of the European Union

** This presentation arises from the Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (EU-JAMRAI), which has received funding from the European Union in the framework of the Health Program (2014-2020) under the Grant Agreement N° 761296. Sole responsibility lies with the author and the Consumers, Health, Agriculture and Food Executive Agency is not responsible for any use that may be made of in the information contained therein.*