

THE JOURNAL OF LAW, MEDICINE & ETHICS

Special Supplement to Volume 46:2 • Summer 2018

A Journal of the American Society of Law, Medicine & Ethics • www.aslme.org



SYMPOSIUM

Incentives to Stimulate Research and Development of New Antibiotics: Detailed Assessments of Select Incentives and Models

GUEST EDITED BY Esther Bettiol, Judith Hackett,
and Stephan Harbarth

- 66 **Diagnosis Confirmation Model: A Value-Based Pricing Model for Inpatient Novel Antibiotics**
Ka Lum, Taimur Bhatti, Silas Holland, Mark Guthrie, and Stephanie Sassman
- 75 **Encouraging Sustainable Use of Antibiotics: A Commentary on the DRIVE-AB Recommended Innovation Incentives**
Chantal M. Morel and Suzanne E. Edwards
- 81 **Should Antibiotics Be Controlled Medicines? Lessons from the Controlled Drug Regimen**
Live Storehagen, Friha Aftab, Christine Årdal, Miloje Savic, and John-Arne Røttingen
- 5 **INTRODUCTION**
Stimulating Research and Development of New Antibiotics While Ensuring Sustainable Use and Access: Further Insights from the DRIVE-AB Project and Others
Esther Bettiol, Judith Hackett, and Stephan Harbarth
- 9 **A Grant Framework as a Push Incentive to Stimulate Research and Development of New Antibiotics**
Miloje Savic and Christine Årdal
- 25 **Antibiotic Pipeline Coordinators**
Enrico Baraldi, Olof Lindahl, Miloje Savic, David Findlay, and Christine Årdal
- 32 **Simulating Market Entry Rewards for Antibiotics Development**
Christopher Okhravi, Simone Callegari, Steve McKeever, Carl Kronlid, Enrico Baraldi, Olof Lindahl, and Francesco Ciabuschi
- 43 **Designing a Delinked Incentive for Critical Antibiotics: Lessons from Norway**
Christine Årdal, Jostein Johnsen, and Karianne Johansen
- 50 **Implementation of a Market Entry Reward within the United States**
Gregory W. Daniel, Monika Schneider, Marianne Hamilton Lopez, and Mark B. McClellan
- 59 **A Perspective on Incentives for Novel Inpatient Antibiotics: No One-Size-Fits-All**
Taimur Bhatti, Ka Lum, Silas Holland, Stephanie Sassman, David Findlay, and Kevin Outterson

jime.sagepub.com

ISSN: 1073-1105



The Journal of Law, Medicine & Ethics (JLME): Material published in *The Journal of Law, Medicine & Ethics (JLME)* contributes to the educational mission of the American Society of Law, Medicine & Ethics, covering public health, health disparities, patient safety and quality of care, and biomedical science and research, and more.

Editorial Office

Journal of Law, Medicine & Ethics, 765 Commonwealth Avenue, Suite 1704, Boston, MA 02215 USA
Phone: 617-262-4990; Fax: 617-437-7596
E-mail: thutchinson@aslme.org

Letters to the Editors: Comments on articles in the Journal should be addressed to the Editor at the editorial office or emailed to thutchinson@aslme.org.

Submission Guidelines: For submission guidelines, please contact the editorial office at thutchinson@aslme.org. Submission guidelines are also available online at <http://journals.sagepub.com/home/lme>.

The Journal of Law, Medicine & Ethics (ISSN 1073-1105) (J812) is published quarterly—in March, June, September and December—by SAGE Publishing, 2455 Teller Road, Thousand Oaks, CA 91320 in association with the American Society of Law, Medicine & Ethics. Send address changes to the Journal of Law, Medicine & Ethics, c/o SAGE Publishing, 2455 Teller Road, Thousand Oaks, CA 91320.

Copyright © 2018, the American Society of Law, Medicine & Ethics. All rights reserved. No portion of the contents may be reproduced in any form without written permission from the publisher.

Subscription Information: All subscription inquiries, orders, back issues, claims, and renewals should be addressed to SAGE Publishing, 2455 Teller Road, Thousand Oaks, CA 91320; telephone: (800) 818-SAGE (7243) and (805) 499-0721; fax: (805) 375-1700; e-mail: journals@sagepub.com; website: journals.sagepub.com. Subscription Price: Institutions: \$962. For all customers outside the Americas, please visit <http://www.sagepub.co.uk/customerCare.nav> for information. Claims: Claims for undelivered or damaged copies must be made no later than six months following month of publication. The publisher will supply replacement issues when losses have been sustained in transit and when the reserve stock will permit.

Member Subscription Information: American Society of Law, Medicine & Ethics member inquiries, change of address, back issues, claims, and membership renewal requests should be addressed to Membership Director, American Society of Law, Medicine & Ethics, 765 Commonwealth Avenue, Suite 1704, Boston, MA 02215; telephone: (617) 262-4990 ext. 15; fax: (617) 437-7597. Requests for replacement issues should be made within six months of the missing or damaged issue. Beyond six months and at the request of the American Society of Law, Medicine & Ethics, the publisher will supply replacement issues when losses have been sustained in transit and when the reserve stock permits.

Copyright Permission: To request permission for reprinting, reproducing, or distributing material from this journal, please visit the desired article on the SAGE Journals website (journals.sagepub.com) and click "Permissions." For additional information, please see www.sagepub.com/journals/permissions.nav.

Advertising and Reprints: Current advertising rates and specifications may be obtained by contacting the advertising coordinator in the Thousand Oaks office at (805) 410-7772 or by sending an e-mail to advertising@sagepub.com. To order reprints, please e-mail reprint@sagepub.com. Acceptance of advertising in this journal in no way implies endorsement of the advertised product or service by SAGE, the journal's affiliated society(ies), or the journal editor(s). No endorsement is intended or implied. SAGE reserves the right to reject any advertising it deems as inappropriate for this journal.

Supplements: Address all correspondence to Barbara Eisenberg, SAGE Publishing, Thousand Oaks, California 91320, (805) 410-7763 (phone), reprint@sagepub.com (e-mail).

Change of Address for Non-Members: Six weeks' advance notice must be given when notifying of change of address. Please send the old address label along with the new address to the SAGE office address above to ensure proper identification. Please specify the name of the journal.

THE JOURNAL OF
LAW, MEDICINE & ETHICS
SPECIAL SUPPLEMENT TO VOLUME 46:2 • SUMMER 2018

BOARD OF EDITORS

Anita Allen-Castellitto, J.D., Ph.D.
University of Pennsylvania Law School

Wendy K. Mariner, J.D., LL.M., M.P.H.
Boston University School of Public Health

R. Alta Charo, J.D.
University of Wisconsin Law School

Maxwell J. Mehlman, J.D.
Case Western Reserve University

Ellen Wright Clayton, M.D., J.D.
Vanderbilt University School of Medicine

E. Haavi Morreim, Ph.D.
University of Tennessee College of Medicine

Bernard M. Dickens, Ph.D., LL.D., LL.M.
University of Toronto Faculty of Law

Thomas H. Murray, Ph.D.
The Hastings Center

Barry Furrow, J.D.
Drexel University Earle Mack School of Law

Wendy E. Parmet, J.D.
Northeastern University School of Law

Jay A. Gold, M.D., J.D., M.P.H.
MetaStar, Inc.

Karen H. Rothenberg, J.D., M.P.A.
University of Maryland School of Law

Lawrence O. Gostin, J.D., LL.D. (Hon.)
*Georgetown University Law Center
Johns Hopkins University*

Margaret A. Somerville, A.M., FRSC
McGill University

Ana Smith Iltis, Ph.D.
Wake Forest University

Daniel P. Sulmasy, O.F.M., M.D., Ph.D.
University of Chicago

Nancy M. P. King, J.D.
Wake Forest School of Medicine

Susan M. Wolf, J.D.
University of Minnesota Law School

John D. Lantos, M.D.
Children's Mercy Hospital

Stuart J. Youngner, M.D.
Case Western Reserve University

THE JOURNAL OF
LAW, MEDICINE & ETHICS
C O N T E N T S

SPECIAL SUPPLEMENT TO VOLUME 46:2 • SUMMER 2018

Symposium Articles

SYMPOSIUM

**Incentives
to Stimulate
Research and
Development
of New
Antibiotics:
Detailed
Assessments of
Select Incentives
and Models**

Guest edited by
Esther Bettiol,
Judith Hackett, and
Stephan Harbarth

1
*Letter from
the Editor*

Cover image ©gettyimages

5

INTRODUCTION

Stimulating Research and Development of New Antibiotics While Ensuring Sustainable Use and Access: Further Insights from the DRIVE-AB Project and Others
Esther Bettiol, Judith Hackett, and Stephan Harbarth

Global discussions are ongoing on how to stimulate antibiotic research and development in order to provide patients with new antibiotics able to address the challenges of antimicrobial resistance. In this supplement, we present nine articles derived from the research performed as part of the Innovative Medicine Initiative-funded DRIVE-AB project and others. These publications provide new evidence and arguments in the debate around economic incentives to stimulate antibiotic innovation, including characteristics, implementation and governance.

9

A Grant Framework as a Push Incentive to Stimulate Research and Development of New Antibiotics
Miloje Savic and Christine Årdal

Antibiotic research and development (R&D) has failed to produce innovative antibiotics in the past two decades, which is due to both scientific and economic factors. We reviewed national and international funding agencies and critically assessed current grant funding mechanisms. Finally, we propose four complementary grant-funding incentives aimed to help developers along the R&D pipeline. Equally important objective of these incentives is to address some of the known R&D risks and bottlenecks.

25

Antibiotic Pipeline Coordinators
Enrico Baraldi, Olof Lindahl, Miloje Savic, David Findlay, and Christine Årdal

The World Health Organization (WHO) has published a global priority list of antibiotic-resistant bacteria to guide research and development (R&D) of new antibiotics. Every pathogen on this list requires R&D activity, but some are more attractive for private sector investments, as evidenced by the current antibacterial pipeline. A "pipeline coordinator" is a governmental/non-profit organization that closely tracks the antibacterial pipeline and actively supports R&D across all priority pathogens employing new financing tools.

32

Simulating Market Entry Rewards for Antibiotics Development
Christopher Okhravi, Simone Callegari, Steve McKeever, Carl Kronlid, Enrico Baraldi, Olof Lindahl, and Francesco Ciabuschi

We design an agent based Monte Carlo model of antibiotics research and development (R&D) to explore the effects of the policy intervention known as Market Entry Reward (MER) on the likelihood that an antibiotic entering pre-clinical development reaches the market. By means of sensitivity analysis we explore the interaction between the MER and four key parameters: projected net revenues, R&D costs, venture capitalists discount rates, and large pharmaceutical organizations' financial thresholds. We show that improving revenues may be more efficient than reducing costs, and thus confirm that this pull-based policy intervention effectively stimulates antibiotics R&D.

Symposium articles are solicited by the guest editor for the purposes of creating a comprehensive and definitive collection of articles on a topic relevant to the study of law, medicine and ethics. Each article is peer reviewed.

Independent articles are essays unrelated to the symposium topic, and can cover a wide variety of subjects within the larger medical and legal ethics fields. These articles are peer reviewed.

Columns are written or edited by leaders in their fields and appear in each issue of *JLME*.

Next Issue:

The Medicalization of Poverty

A Symposium Guest Edited by Robin Fretwell Wilson and Lois Shepherd

43

Designing a Delinked Incentive for Critical Antibiotics: Lessons from Norway
Christine Årdal, Jostein Johnsen, and Karianne Johansen

No country has yet implemented a pilot to ensure access to or the innovation of new antibiotics for multi-drug infections. A team from national health agencies in Norway, with the support of the Innovative Medicine Initiative-funded project DRIVE-AB, designed a model suitable for the national context, including the selection of the antibiotics, the potential value, and the operational model.

50

Implementation of a Market Entry Reward within the United States
Gregory W. Daniel, Monika Schneider, Marianne Hamilton Lopez, and Mark B. McClellan

As part of a multifactorial approach to address weak incentives for innovative antimicrobial drug development, market entry rewards (MERs) are an emerging solution. Recently, the Duke-Margolis Center for Health Policy released the Priority Antimicrobial Value and Entry (PAVE) Award proposal, which combines a MER with payment reforms, transitioning from volume-based to “value-based” payments for antimicrobials. Here, the PAVE Award and similar MERs are reviewed, focusing on further refinement and avenues for implementation.

59

A Perspective on Incentives for Novel Inpatient Antibiotics: No One-Size-Fits-All
Taimur Bhatti, Ka Lum, Silas Holland, Stephanie Sassman, David Findlay, and Kevin Outterson

The need for new “pull” incentives to stimulate antibiotic R&D is widely recognized. Due to the global diversity of health systems, combined with different challenges faced by antibiotics used in different types of healthcare settings, there is no one-size-fits-all solution. Instead, different “pull” incentives should be tailored to local contexts, priorities, and antibiotic types. Policymakers and industry should collaborate to identify appropriate solutions at the local, regional, and global levels.

66

Diagnosis Confirmation Model: A Value-Based Pricing Model for Inpatient Novel Antibiotics
Ka Lum, Taimur Bhatti, Silas Holland, Mark Guthrie, and Stephanie Sassman

The Diagnosis Confirmation Model (DCM) includes a dual-pricing mechanism designed to support value-based pricing of novel antibiotics while improving the alignment of financial incentives with their optimal use in patients at high risk of drug-resistant infections. DCM is a market-based model and complementary to delinked models. Policymakers interested in stimulating antibiotic innovation could consider tailoring the DCM to their reimbursement systems and incorporating it into the suite of incentives to improve the economics of antibiotics.

75

Encouraging Sustainable Use of Antibiotics: A Commentary on the DRIVE-AB Recommended Innovation Incentives
Chantal M. Morel and Suzanne E. Edwards

The ability to sustain antibiotic efficacy is directly affected by incentive models aiming to stimulate antibiotic research and development. This paper analyzes the extent to which the models proposed by the Innovative Medicine Initiative-funded research project DRIVE-AB can be expected to support sustainable use, drawing on basic economic theory and the incentives that derive from it. It then discusses the use of minimal safeguards that will be needed to support sustainable use where industry incentives have not been re-aligned with those of public health.

81

Should Antibiotics Be Controlled Medicines? Lessons from the Controlled Drug Regimen
Live Storehagen, Friha Aftab, Christine Årdal, Miloje Savic, and John-Arne Røttingen

This study aimed to identify the antibiotic-relevant lessons from the controlled drug regimen for narcotics. Whereas several elements of the United Nations Single Convention on Narcotic Drugs (1961) could be advantageous for antibiotics, we doubt that an international legally binding agreement for controlling antibiotic consumption would be any more effective than implementing stewardship measures through national AMR plans.