Göteborg, 2016

Antibiotic resistance in the environment:
a contribution from metagenomic studies

av **Johan Bengtsson-Palme**

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet, kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg, torsdagen den 26 maj 2016, klockan 9.00.

Fakultetsopponent:
Professor Thomas Berendonk
Institüt für Hydrobiologie, Technische Universität Dresden, Tyskland

Avhandlingen baseras på följande delarbeten

I. **Metaxa2: improved identification and taxonomic classification of small and large subunit rRNA in metagenomic data**
Bengtsson-Palme J, Hartmann M, Eriksson KM, Pal C, Thorell K, Larsson DGJ, Nilsson RH
Molecular Ecology Resources 15, 6, 1403–1414 (2015)

II. **Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation**
Bengtsson-Palme J, Larsson DGJ
Environment International 86, 140-149 (2016)

III. **Minimal selective concentrations of tetracycline in complex aquatic bacterial biofilms**
Lundström SV, Östman M, Bengtsson-Palme J, Rutgersson C, Thoudal M, Sircar T, Blanck H, Eriksson KM, Tysklind M, Flach C-F, Larsson DGJ
Science of the Total Environment 553, 587–595 (2016)

IV. **Elucidating selection processes for antibiotic resistance in sewage treatment plants using metagenomics**
Bengtsson-Palme J, Hammarén R, Pal C, Östman M, Björlenius B, Flach C-F, Fick J, Kristiansson E, Tysklind M, Larsson DGJ
Manuscript

V. **Shotgun metagenomics reveals a wide array of antibiotic resistance genes and mobile elements in a polluted lake in India**
Bengtsson-Palme J, Boulund F, Fick J, Kristiansson E, Larsson DGJ
Frontiers in Microbiology 5, 648 (2014)

VI. **The human gut microbiome as a transporter of antibiotic resistance genes between continents**
Bengtsson-Palme J, Angelin M, Huss M, Kjellqvist S, Kristiansson E, Palmgren H, Larsson DGJ, Johansson A
Antimicrobial Agents and Chemotherapy 59, 10, 6551-6560 (2015)

VII. **Antibiotic resistance genes in the environment: prioritizing risks**
Bengtsson-Palme J, Larsson DGJ
Nature Reviews Microbiology 13, 369 (2015)

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR BIOMEDICIN

GÖTEBORGS UNIVERSITET

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Antibiotic resistance in the environment: a contribution from metagenomic studies

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Abstract

Antibiotic resistance accounts for hundreds of thousands of deaths annually, and its projected increase has made the WHO recognize it as a major global health threat. In the last decade, evidence has mounted suggesting that the environment plays an important role in the progression of resistance. The external environment acts as a source of resistance genes for human pathogens, but is also an important dissemination route allowing the spread of resistant bacteria between different environments and human populations. In this thesis, large-scale DNA sequencing techniques are used to gain a better understanding of the risks associated with environmental antibiotic resistance. A key task in this process is the quantification of the number of antibiotic resistance genes in different environments using metagenomics. However, equally important is to put this information into a larger perspective, by including, for example, taxonomic data, concentrations of antibiotics present, and the genomic contexts of identified resistance genes. This thesis presents a software tool – Metaxa2 – for improved taxonomic analysis of shotgun metagenomic data, which is shown to give more accurate taxonomic classifications of short read data than other tools (Paper I). It also provides theoretically predicted no-effect concentrations for 111 antibiotics (Paper II), and experimentally determined minimal selective concentrations for tetracycline (Paper III). Furthermore, resistance genes are quantified in two environments suggested to pose selective conditions for resistance: sewage treatment plants (Paper IV) and a lake exposed to waste from pharmaceutical production (Paper V). There was no clear evidence for selection of antibiotic resistance genes in sewage treatment plants, however other factors such as oxygen availability seem to have much stronger effects on these microbial communities, which may mask small selective effects of antibiotics and other co-selective agents. In contrast, in the lake subjected to industrial pharmaceutical pollution, resistance genes and mobile genetic elements were both diverse and abundant. Finally, Paper VI shows that travel contributes to the spread of resistance genes against several different classes of antibiotics between countries with higher resistance rates and Sweden. In Papers IV–VI, the genetic contexts of resistance genes were assessed through metagenomic assembly, showing how different resistance genes are linked to each other in different environments. Through these means, the thesis contributes knowledge about risk settings for development and transmission of antibiotic resistance genes, which can be used to guide risk assessment and management schemes to delay or reduce clinical resistance development.

Keywords: antibiotic resistance, metagenomics, bioinformatics, next generation sequencing, resistance selection

ISBN: 978-91-628-9758-1 (TRYCK) http://hdl.handle.net/2077/41843
ISBN: 978-91-628-9759-8 (PDF)