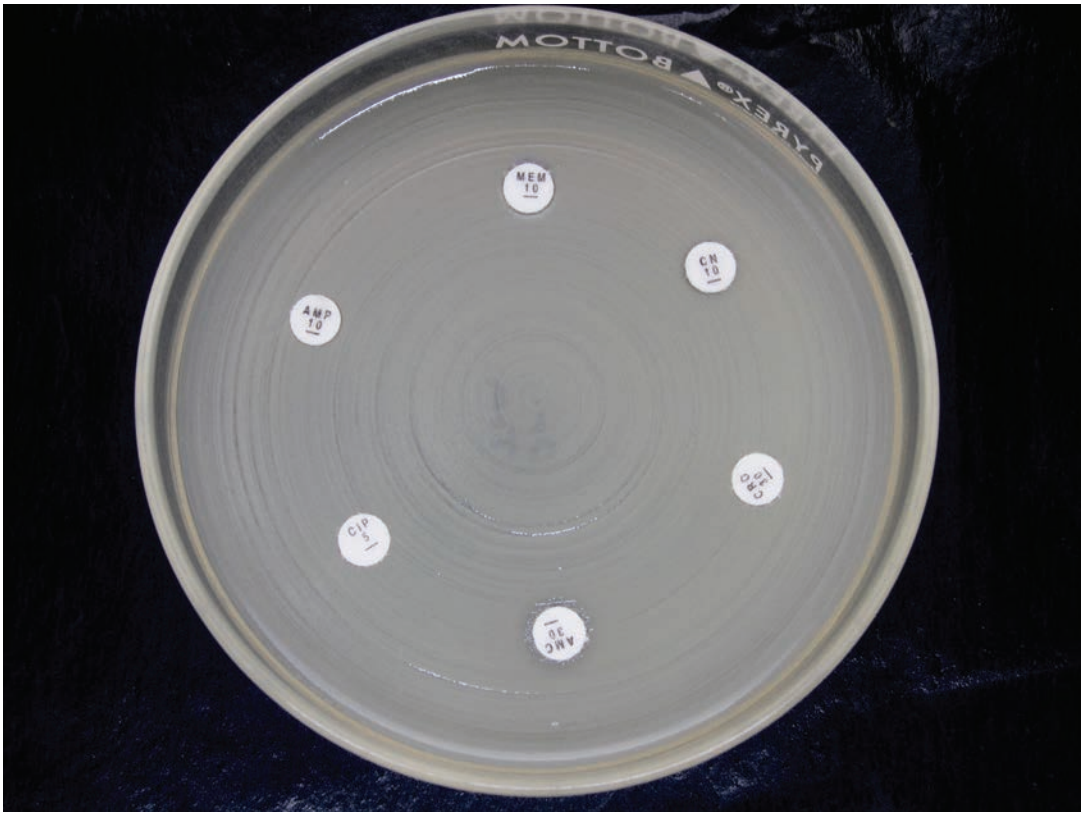
Lao - Oxford - Mahosot Hospital - Wellcome Trust Research Unit

SCIENTIFIC ANNUAL REPORT FOR 2017

LAO-OXFORD-MAHOSOT HOSPITAL-WELLCOME TRUST RESEARCH UNIT (LOMWRU)
MICROBIOLOGY LABORATORY
MAHOSOT HOSPITAL
VIENTIANE, LAO PDR

TO

MINISTRY OF HEALTH
GOVERNMENT OF THE LAO PDR



Antibiotic susceptibility testing of a multi-drug resistant *Escherichia coli* isolated from the urine of a 51 year old Lao patient with a perinephric abscess. There are no inhibition zones surrounding any of the antibiotic disks, including meropenem (MEM, 12 o'clock position), a 'last-line' antibiotic. Whole-genome sequencing confirmed that this isolate was carrying a NDM-5 carbapenemase. Such infections are likely to become more frequent, given the ability of carbapenemases to spread and the increasing availability of meropenem in Laos.

CONTENTS

Re-Opening of the Microbiology Laboratory at Mahosot Hospital by HE The Minister of Health, Professor Dr Bounkong Syhavong, HE The UK Ambassador, Mr Hugh Evans, Director of Mahosot Hospital, Professor Dr Bounthapany Bounxouei and the Director of the MORU Network, Professor Nicholas Day on 31st May 2017

ບົດສັງລວມຫຍໍ້

ກ. ໂຄງການຄົ້ນຄວ້າພະຍາດເຂດຮ້ອນລະຫວ່າງໂຮງໝໍມະໂຫສົດ-ແອວຄຳຕູ້ສ-ມະຫາວິທະຍາໄລອ໋ອກຟອດ ຫຼື The Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit (LOMWRU) ເປັນໜ່ວຍງານຄົ້ນຄວ້າທາງຄລີນິກ ເຊິ່ງນອນຢູ່ໃນພະແນກວິເຄາະຈຸລິນຊີ, ໂຮງໝໍມະໂຫສົດ. ໂຄງການນີ້ ຖືກສ້າງຕັ້ງຂຶ້ນໃນປີ 2000 ພາຍໃຕ້ເຄືອຂ່າຍຂອງ MORU Tropical Network ແລະ ຕິດພັນຢ່າງຊະນິດແໜ້ນກັບໜ່ວຍງານຄົ້ນຄວ້າພະຍາດເຂດຮ້ອນມະຫາວິທະຍາໄລມະຫິດົນ-ອ໋ອກຟອດ ປະຈຳບ້ານກອກ (MORU-Bangkok) ແລະ ປະມານ 41% ຂອງວຽກຄົ້ນຄວ້າຂອງພວກເຮົາ ແມ່ນໄດ້ຕິດພັນກັບໜ່ວຍງານດັ່ງກ່າວ.

ຂ. ໂຄງການ LOMWRU ໄດ້ຮັບທຶນຊ່ວຍເຫລືອຫລັກ ຈາກທາງແອວຄຳຕູ້ສ ປະເທດ ອັງກິດ ແລະ ທຶນອີກສ່ວນໜຶ່ງແມ່ນໄດ້ຈາກ US Naval Medical Research Centre, the Bill & Melinda Gates Foundation, The European Union, Department for International Development-UK (DFID), New Zealand e-Asia, Fondation Total/Institute Pasteur, Global Good, DTRA, Global Antibiotic Research Partnership ແລະ the Asian Development Bank. ນອກນີ້ ທາງໂຄງການຍັງໄດ້ຮັບການຊ່ວຍເຫລືອເປັນເຄື່ອງອຸປະກອນ ຈາກສະຖາບັນຄົ້ນຄວ້າເພື່ອການພັດທະນາ/ມະຫາວິທະຍາໄລແອ໋ກຊ-ມາກໄຊ ປະເທດຝລັ່ງ ແລະ ໂຄງການຄົ້ນຄວ້າພະຍາດຣິກເກັດເຊຍ ຂອງສູນຄົ້ນຄວ້າທາງການແພດກອງທັບເຮືອ ສະຫະລັດອາເມລິກາ.

ຄ. ພະແນກວິເຄາະຈຸລິນຊີ ມີພະນັກງານ (ພາກລັດ) ທັງໝົດ 29 ຄົນ, ສ່ວນ LOMWRU ມີພະນັກງານໂຄງການ 49 ຄົນ, ໃນນີ້ 88% ແມ່ນຄົນລາວ ແລະ 56% ເປັນເພດຍິງ. ພວກເຮົາມີຫ້ອງວິເຄາະຈຸລະຊີວະວິທະຍາທາງຄລີນິກ, ຫ້ອງວິເຄາະທາງພັນທຸກຳ, ຫ້ອງວິເຄາະເຊໂຣໂລຊີ, ແລະ ຫ້ອງວິເຄາະລະດັບ 3 (BSL3). ການປະຕິບັດງານໃນຫ້ອງວິເຄາະດັ່ງກ່າວ ແມ່ນເປັນໄປຕາມແນວທາງ-ລະບຽບການຄວາມປອດໄພ ຂອງມະຫາວິທະຍາໄລອ໋ອກຟອດ.

ງ. LOMWRU ຊ່ວຍບໍລິການບ່ຽມະຕິພະຍາດຊຶມເຊື້ອພາຍໃນໂຮງມະໂຫສົດ ແລະ ໂຮງໝໍຕ່າງແຂວງ ເຊັ່ນ ໂຮງໝໍແຂວງ ຫລວງນ້ຳທາ, ສາລະວັນ ແລະ ຊຽງຂວາງ, ເຮັດການຄົ້ນຄວ້າທາງຄລີນິກ, ແລະ ສ້າງຄວາມເຂັ້ມແຂງໃຫ້ແກ່ພະນັກງານພາກລັດໃນດ້ານການບ່ຽມະຕິພະຍາດ ແລະ ການເຮັດຄົ້ນຄວ້າ ໂດຍຜ່ານການຝຶກອົບຮົມ ແລະ ປະຕິບັດງານຕົວຈິງ. LOMWRU ຍັງມີການຮ່ວມມືກັບສູນໄຂ້ຍູງ, ແມ່ກາຝາກ ແລະ ແມງໄມ້ ເຮັດໂຄງການຄົ້ນຄວ້າຢູ່ 5 ແຂວງພາກໃຕ້, ຮ່ວມມືກັບກົມອາຫານ ແລະ ຢາ ໂດຍສະເພາະພາກສ່ວນກວດກາ ແລະ ສູນວິໄຈອາຫານ ແລະ ຢາ ດຳເນີນໂຄງການຄົ້ນຄວ້າກ່ຽວກັບຄຸນນະພາບຂອງຢາ, ແລະ ມີໂຄງການຮ່ວມມືກ່ຽວກັບເຊື້ອຈຸລິນຊີຕ້ານຕ່ຢາຕ້ານເຊື້ອ ຮ່ວມກັບກົມຄວບຄຸມພະຍາດຕິດຕໍ່ ກະຊວງສາທາລະນະສຸກ.

ຈ. ຈຸດສຸມສຳລັບວຽກຄົ້ນຄວ້າຂອງພວກເຮົາໄດ້ແກ່ ສາເຫດ ແລະ ລະບາດວິທະຍາຂອງໄຂ້, ລັກສະນະການຕ້ານຂອງເຊື້ອພະຍາດຕ່ຢາປິ່ນປົວ ລວມທັງການບ່ຽມະຕິ ແລະ ປົ່ວປົວທີ່ສົມເຫດສົມຜົນ ເຊິ່ງທັງໝົດນີ້ແມ່ນແນໃສ່ເພື່ອສະໜອງຂໍ້ມູນສຳລັບສ້າງເປັນນະໂຍບາຍດ້ານສາທາລະນະສຸກໃນຂົງເຂດອາຊີ ແລະ ດ້ານຢາປິ່ນປົວໃນລະດັບສາກົນ.

ສ. ໃນປີ 2017 ທາງໂຄງການໄດ້ສະໜັບສະໜູນພະນັກງານລາວຈຳນວນ 12 ຄົນ ເຂົ້າຮ່ວມກອງປະຊຸມຢູ່ຕ່າງປະເທດຈຳນວນ 6 ຄັ້ງ ແລະ ໄດ້ໃຫ້ການສະໜັບສະໜູນພະນັກງານພາກລັດ 3 ຄົນ ສຶກສາຕໍ່ໃນລະດັບປະລິຍາເອກ ແລະ ປະລິນຍາໂທ ຢູ່ມະຫາວິທະຍາໄລມະຫິດົນ ແລະ ມະຫາວິທະຍາໄລອຳສະເຕີດຳ ປະເທດ ຮອນແລນ, ແລະ ອີກ 1 ຄົນ ສຶກສາໃນລະດັບປະລິນຍາຕີ ທີ່ມະຫາວິທະຍາໄລຂອນແກ່ນ.

ຊ. ໃນປີ 2017 ພວກເຮົາໄດ້ຕີພິມ ຫລື ກຳລັງຖືກຮັບຕີພິມເຜີຍແຜ່ຜົນຂອງການຄົ້ນຄວ້າລົງໃນວາລະສານການແພດສາກົນ ຈຳນວນ 43 ບົດ, ເຊິ່ງໃນນີ້ ມີ 39 ບົດຖືກພິມເຜີຍແຜ່ໃນວາລະສານທີ່ມີການທົບທວນຄັກແນ່, ເປັນຈົດໝາຍເຫດ 1 ບົດ, ພິມລົງໃນປຶ້ມຕຳລາທາງການແພດຈຳນວນ 3 ພາກ. ນັບຕັ້ງແຕ່ໂຄງການຖືກສ້າງຕັ້ງເປັນຕົ້ນມາ, ນັກຄົ້ນຄວ້າຂອງໂຄງການ LOMWRU ມີຜົນງານຕີພິມເຜີຍແຜ່ຜົນການຄົ້ນຄວ້າ ທັງໝົດ 333 ບົດ ລວມທັງປຶ້ມຕຳລາຕ່າງໆ.

ຍ. ຜົນການຄົ້ນຄວ້າຜ່ານມາຂອງ LOMWRU ທີ່ຖືກນຳໄປຜັນຂະຫຍາຍ ເປັນແນວທາງນະໂຍບາຍ ດ້ານສາທາລະນະສຸກ ພາຍໃນປະເທດ ລວມມີ: ການຈັດຕັ້ງປະຕິບັດການສັກຢາກັນພະຍາດທີ່ເກີດຈາກເຊື້ອ Pneumococcus ແລະ ການສັກຢາກັນພະຍາດອັກເສບສະໝອງຍີ່ປຸ່ນ, ການປ່ຽນແປງແນວທາງການປິ່ນປົວພະຍາດໄຂ້ຍູງ ແລະ ພະຍາດໄຂ້ທໍລະພິດ (Typhoid). ນອກນີ້ ພວກເຮົາຍັງໄດ້ຄົ້ນພົບພະຍາດທີ່ສຳຄັນບາງຢ່າງເປັນຄັ້ງທຳອິດໃນປະເທດລາວ, ໄດ້ຊີ້ໃຫ້ເຫັນຄວາມສຳຄັນຂອງພະຍາດໄຂ້ແມງແດງ, ໄຂ້ຢ່ຽວໜູ, ໄຂ້ທໍລະພິດ, ເມລີອອຍໂດສຊິສ, ແລະ ອັກເສບສະໝອງຍີ່ປຸ່ນ ເຊິ່ງເຮັດໃຫ້ພວກເຮົາເຂົ້າໃຈຢ່າງເລິກເຊິ່ງຕື່ມ ກ່ຽວກັບລັກສະນະດ້ານລະບາດວິທະຍາ ແລະ ແນວທາງການປ້ອງກັນພະຍາດດັ່ງກ່າວ.

ດ. ສະຫລຸບຜົນຂອງການຄົ້ນຄວ້າທີ່ມີຄວາມໝາຍສຳຄັນ ຕໍ່ປະເທດລາວ ທີ່ໄດ້ຕີພິມເຜີຍແຜ່ ຫລື ກຳລັງຈະຖືກຕີພິມເຜີຍແຜ່ ໃນປີ 2017 ມີດັ່ງຕໍ່ໄປນີ້ (ກະລຸນາເບິ່ງລາຍລະອຽດຕື່ມໃນບົດລາຍງານ):

*** ລັກສະນະການຕ້ານຂອງເຊື້ອຈຸລິນຊີ ຕໍ່ຢາຕ້ານເຊື້ອ ກຳລັງເປັນບັນຫາສຳຄັນດ້ານສາທາລະນະສຸກ ແລະ ກໍ່ໃຫ້ເກີດຄວາມກັງວົນນັບມື້ຫລາຍຂຶ້ນໃນ ສປປ ລາວ ກໍ່ຄືໃນທົ່ວໂລກ.**

- ບັນຫາການຕ້ານ (ການດື້) ຂອງເຊື້ອ Enterobacteriaceae ຕໍ່ຢາຕ້ານເຊື້ອໃນກຸ່ມ Beta-lactamin (ESBL) ແລະ ຕ້ານຕໍ່ຢາຕ້ານເຊື້ອຫລາຍຕົວ ເປັນສາເຫດການຊຶມເຊື້ອສຳຄັນ ທີ່ພົບເຫັນນັບມື້ຫລາຍຂຶ້ນໃນໂຮງໝໍມະໂຫສົດ. ອັນນີ້ຖືເປັນບັນຫາເຊື້ອຈຸລິນຊີຕ້ານຕໍ່ຢາຕ້ານເຊື້ອທີ່ພົບເຫັນເລື້ອຍທີ່ສຸດ ໃນຫ້ອງວິເຄາະຈຸລິນຊີວິທະຍາຂອງພວກເຮົາ ເນື່ອງຈາກອັດຕາການກວດພົບໃນໂຮງໝໍ ແມ່ນເພີ່ມຂຶ້ນເລື້ອຍໆ ແລະ ເຊື້ອດັ່ງກ່າວກໍຕ້ານຕໍ່ຢາຕ້ານເຊື້ອທີ່ມັກໃຊ້ເປັນປະຈຳ ເຊັ່ນ cephalosporins and penicillins ແລະ ຍັງພົບວ່າ ມີການຕ້ານຕໍ່ຢາ gentamicin and ciprofloxacin/ofloxacin ເລື້ອຍໆ. ພວກເຮົາພົບເຫັນເຊື້ອດັ່ງກ່າວໃນຄົນເຈັບບາງຈຳນວນ ແລະ ເຊື້ອກໍຕ້ານຕໍ່ຢາຕ້ານເຊື້ອເກືອບທຸກຕົວ ເຮັດໃຫ້ພວກເຮົາກັງວົນວ່າ ພວກເຮົາຈະບໍ່ມີຢາທີ່ສາມາດປິ່ນປົວ-ຂ້າເຊື້ອໄດ້ໃນອະນາຄົດ ຫລື ຖ້າມີກໍຕ້ອງໃຊ້ຢາທີ່ມີລາຄາແພງທີ່ສຸດ ເຊິ່ງຄົນເຈັບອາດບໍ່ສາມາດຈ່າຍໄດ້.
- ທີ່ໜ້າແປກໃຈກໍຄືວ່າ ESBL bacteria ຍັງພົບເຫັນເປັນປະຈຳໃນລຳໃສ້ຂອງຄົນ ແລະ ສັດ ທີ່ມີສຸຂະພາບແຂງແຮງພາຍໃນບ້ານແຫ່ງໜຶ່ງ ຢູ່ເຂດຫ່າງໄກສອກຫລີກຂອງແຂວງຊຽງຂວາງ ເຊິ່ງຂໍ້ມູນນີ້ຊີ້ໃຫ້ເຫັນວ່າ ESBL ເປັນບັນຫາຢູ່ຊຸມຊົນບົດຂອງລາວເຮົາແລ້ວ ແລະ ກໍຈະເປັນບັນຫາທີ່ໃຫ່ຍຫລວງໃນອະນາຄົດຖ້າເຮົາບໍ່ມີມາດຕະການຫຍັງ. ສິ່ງໜຶ່ງທີ່ໜ້າແປກໃຈກໍຄືວ່າ ປະຊາກອນພາຍໃນບ້ານດັ່ງກ່າວຈຳນວນຫລາຍສົມຄວນ (13.4%) ໄດ້ຮັບຢາຕ້ານເຊື້ອພາຍໃນ 2 ອາທິດ ກ່ອນໜ້າທີມງານລົງໄປເຮັດການສຳຫລວດພາຍໃນບ້ານ.
- ນອກຈາກນີ້ ພວກເຮົາຍັງພົບວ່າ ຄົນຕ່າງປະເທດທີ່ມາຮ່ວມສຳມະນາທາງການແພດ ໃນນະຄອນຫລວງວຽງຈັນ (ໄດ້ເອົາຕົວຢ່າງອາຈົມໄປກວດທັນທີ ທີ່ມາເຖິງ ແລະ 3 ອາທິດຕໍ່ມາ) ແມ່ນພົບມີເຊື້ອຈຸລິນຊີທີ່ຕ້ານຕໍ່ຢາ cephalosporin ເຊິ່ງຂໍ້ມູນນີ້ຊີ້ໃຫ້ເຫັນວ່າ ເຊື້ອ ESBL ແມ່ນພົບໄດ້ຫລາຍໃນຄົນ ແລະ ສິ່ງແວດລ້ອມຢູ່ວຽງຈັນ, ແລະ ກໍຊີ້ໃຫ້ເຫັນວ່າ ແຂກທີ່ມາຢ້ຽມຢາມ ກໍມີການຕິດເຊື້ອເຂົ້າໃນຕົວ

ຢ່າງໄວວາ ເຊິ່ງເຮັດໃຫ້ມີຄວາມສ່ຽງຕໍ່ສຸຂະພາບຂອງເຂົາເຈົ້າ ແລະ ສ່ຽງຕໍ່ການແຜ່ກະຈາຍເຊື້ອໄປຫາ ບ່ອນອື່ນໆ.

- ພວກເຮົາພົບເຊື້ອ Enterobacteriaceae ທີ່ຕ້ານຕໍ່ຢາ carbapenem ເປັນຄັ້ງທຳອິດໃນ ສປປ ລາວ ເຊິ່ງ ທັງໝົດເປັນເຊື້ອ *E. coli* ທີ່ພົບຢູ່ໃນຕົວຢ່າງໜອງ 1 ເຊື້ອ, ຕົວຢ່າງຈາກລະບົບຖ່າຍເທ 1 ເຊື້ອ ແລະ ຈາກເລືອດ 1 ເຊື້ອ. ນອກຈາກນີ້ຍັງພົບວ່າ ເຊື້ອ Acinetobacters ທີ່ຕ້ານຕໍ່ຢາ carbapenem ກໍ່ພົບເຫັນເປັນປະຈຳໃນຕົວຢ່າງທີ່ໄດ້ຈາກລະບົບຫາຍໃຈຂອງພະແນກມໍລະສູມ ໂຮງໝໍມະໂຫສົດ. ເນື່ອງຈາກວ່າ ກຳລັງມີການລິເລີ່ມໃຊ້ຢາ carbapenems ໃນລາວ, ສະນັ້ນ ການຄົ້ນພົບດັ່ງກ່າວຈຶ່ງເຮັດ ໃຫ້ພວກເຮົາມີຄວາມກັງວົນຫລາຍທີ່ສຸດ ແລະ ມັນຍຸກຮ້ອງໃຫ້ຕ້ອງມີການຕິດຕາມສຳລັບການນຳໃຊ້ ຢາດັ່ງກ່າວຢ່າງເຂັ້ມງວດ.

- ເຊື້ອສາເຫດການຊຶມເຊື້ອເລືອດ ໃນກຸ່ມ non-typhoid Salmonella ທີ່ໂຮງໝໍມະໂຫສົດ ໄດ້ແກ່ ເຊື້ອ *S.* Enteritidis, *S.* Typhimurium and *S.* Choleraesuis ເຊິ່ງສ່ວນໃຫ່ຍມັກຈະຕ້ານຕໍ່ຢາ Ciprofloxacin. ສ່ວນເຊື່ອທີ່ພົບໃນອາຈົມຂອງຄົນເຈັບຖອກທ້ອງແມ່ນມີຫລາຍຊະນິດ ແຕ່ສ່ວນໃຫ່ຍ ແມ່ນພວກ *S.* Typhimurium, *S.* Weltevreden, and *S.* Stanley.

- ໃນຈຳນວນເຊື້ອ *Staphylococcus aureus* 96 Isolates ທີ່ກວດເຫັນ ແມ່ນບໍ່ພົບການຕ້ານຕໍ່ຢາ ຫລາຍປານໃດ ຍົກເວັ້ນການຕ້ານຕໍ່ຢາ penicillin (97%) and tetracycline (50%). ປະມານ 7% ຂອງເຊື້ອດັ່ງກ່າວ ມີການຕ້ານຕໍ່ຢາ Methicillin ເຊິ່ງເອີ້ນວ່າ methicillin-resistant *S. aureus* (MRSA). MRSA ມີທ່າອ່ຽງເພີ່ມຂຶ້ນ ເຊິ່ງເປັນໜ້າກັງວົນຫລາຍສົມຄວນ ເນື່ອງຈາກຈະມີຄວາມ ຫຍຸ້ງຍາກໃນການປິ່ນປົວ. ເປັນຄັ້ງທຳອິດທີ່ພວກເຮົາຄົ້ນພົບເຊື້ອ *S. argenteus* ໃນ ສປປ ລາວ.

- ໃນຂະນະທີ່ຂໍ້ມູນຫລັກຖານຫລາຍຢ່າງຊີ້ບອກວ່າ ມີຄວາມຈຳເປັນຕ້ອງເພີ່ມທະວີເອົາໃຈໃສ່ ເລື່ອງການ ນຳໃຊ້ຢາຕ້ານເຊື້ອ ແລະ ການຄວບຄຸມການຕິດເຊື້ອຢ່າງເຂັ້ມງວດນັ້ນ, ພວກເຮົາພັດຄົ້ນພົບເຊື້ອ *Clostridium difficile* ໃນອາຈົມຂອງຄົນເຈັບຢູ່ໂຮງໝໍມະໂຫສົດ. ການເກີດມີເຊື້ອດັ່ງກ່າວ (ທີ່ເປັນສາ ເຫດສຳຄັນຂອງຖອກທ້ອງໃນໂຮງໝໍ) ແມ່ນບໍ່ແປກເລີຍ ເນື່ອງຈາກມີການນຳໃຊ້ຢາ cephalosporin ຢ່າງແຜ່ຫລາຍໃນໂຮງໝໍແຫ່ງຕ່າງໆຂອງນະຄອນຫລວງວຽງຈັນ.

- ຜົນການທົດສອບເຊື້ອ *N. gonorrhoeae* ໃສ່ຢາຕ້ານເຊື້ອຈຳນວນ 158 ເຊື້ອ ພົບວ່າ: 100% ແມ່ນ ຖືກກັບຢາ ceftriaxone and spectinomycin ແຕ່ພັດມີການຕ້ານໃນລະດັບສູງ ຕໍ່ຢາ ciprofloxacin, penicillin and tetracycline. ຂໍ້ມູນນີ້ ຊີ້ໃຫ້ເຫັນວ່າ ຢາ ceftriaxone and spectinomycin ໜ້າຈະ ມີປະສິດທິພາບສູງຕໍ່ເຊື້ອ *N. gonorrhoeae* ໃນ ສປປ ລາວ. ການຕິດຕໍ່ຫາຄູ່ນອນຂອງຄົນເຈັບທີ່ຕິດ ເຊື້ອ ເພື່ອມາປິ່ນປົວຮ່ວມກັນ ຖືເປັນແນວທາງສຳຄັນສຳລັບການຫລຸດຜ່ອນພະຍາດ ພຕພ.

- ພວກເຮົາກຳລັງເຮັດການສຳຫລວດກ່ຽວກັບຄວາມຊຸກສຳລັບການນຳໃຊ້ຢາຕ້ານເຊື້ອ ແລະ ການຕ້ານ ຂອງເຊື້ອຕໍ່ຢາ ຢູ່ໂຮງໝໍ 4 ແຫ່ງ ຂອງ ສປປ ລາວ. ພວກເຮົາຄາດວ່າ ຂໍ້ມູນຈາກການສຳຫລວດນີ້ ຈະເປັນປະໂຫຍດໃຫ້ແກ່ກະຊວງສາທາລະນະສຸກ ໂດຍສະເພາະໃນເລື່ອງການຄາດຄະເນປະລິມານຢາ ຕ້ານເຊື້ອທີ່ຖືກນຳໃຊ້ໃນຄົນເຈັບທີ່ນອນໂຮງໝໍ ແລະ ເພື່ອໃຊ້ສຳລັບຕິດຕາມການປ່ຽນແປງສະພາບ ການນຳໃຊ້ຢາຕ້ານເຊື້ອ ລວມທັງການນຳໃຊ້ຂໍ້ມູນເພື່ອປັບປ່ຽນແນວທາງການສັ່ງຢາທີ່ສົມເຫດສົມຜົນ ຂອງແພດໝໍ.

- ການແຜ່ຂະຫຍາຍຂອງເຊື້ອຈຸລິນຊີທີ່ຕ້ານຕໍ່ຢາຕ້ານເຊື້ອໃນ ສປປ ລາວ ຈະສົ່ງຜົນສະທ້ອນຢ່າງໃຫ່ຍຫລວງຕໍ່ຄົນເຈັບ, ຊຸມຊົນ ແລະ ເສດຖະກິດ. ສະນັ້ນ ຈຶ່ງມີຄວາມຈຳເປັນຢ່າງຮີບດ່ວນ ທີ່ຈະຕ້ອງເອົາໃຈໃສ່ວຽກງານຄວບຄຸມການຕິດເຊື້ອ, ການນຳໃຊ້ຢາຕ້ານເຊື້ອຢ່າງສົມເຫດສົມຜົນ, ແລະ ລະບຽບຫລັກການຕ່າງໆທີ່ກ່ຽວຂ້ອງ.

- ເພື່ອຊ່ວຍໃຫ້ມີຂໍ້ມູນ-ຫລັກຖານ ແລະ ແນວທາງປະຕິບັດທີ່ເໝາະສົມ, ພວກເຮົາໄດ້ຮ່ວມມືກັບ ກະຊວງສາທາລະນະສຸກ ລວມທັງຄູ່ຮ່ວມງານອື່ນໆໂດຍສະເພາະຄູ່ຮ່ວມງານ GARP (Global Antibiotic Resistance Partnership) ຈັດຕັ້ງທິມງານວິຊາການຄວບຄຸມເຊື້ອຈຸລິນຊີທີ່ຕ້ານຕໍ່ຢາຕ້ານເຊື້ອ ເຊິ່ງທິມງານນີ້ ຈະເຮັດວຽກສົມທົບກັບຄະນະກຳມະການຂອງ WHO/ FAO/OIE. ພວກເຮົາມີແຜນຈັດປະຊຸມສຳຫລັບທິມງານດັ່ງກ່າວໃນເດືອນ ເມສາ 2018 ເພື່ອຫາລືຜົນຂອງການທົບທວນຂໍ້ມູນເຊື້ອຈຸລິນຊີທີ່ຕ້ານຕໍ່ຢາຕ້ານເຊື້ອ ໃນ ສປປ ລາວ.

- ພວກເຮົາກຳລັງພັດທະນາລະບົບຕາຕະລາງ ແລະ ແຜນທີ່ສຳລັບຂໍ້ມູນຄຸນນະພາບຂອງຢາຕ້ານເຊື້ອໃນທົ່ວໂລກ ເຊິ່ງຈະຊ່ວຍສຳລັບການສຶກສາ ແລະ ເຮັດ modelling ເພື່ອຫາຄວາມສຳພັນລະຫວ່າງຄຸນນະພາບຂອງຢາ ແລະ ລັກສະນະການຕ້ານຂອງເຊື້ອຈຸລິນຊີຕໍ່ຢາຕ້ານເຊື້ອ.

* ໄຂ້ມາລາເຣຍ ແລະ ຄວາມສຳຄັນໃນການກຳຈັດພະຍາດດັ່ງກ່າວອອກຈາກ ສປປ ລາວ

- ພວກເຮົາກຳລັງສືບຕໍ່ເຝົ້າລະວັງ ລັກສະນະການຕ້ານຂອງເຊື້ອກາຝາກມາລາເຣຍ ທາງດ້ານພັນທຸກຳຮ່ວມກັບສູນໄຂ້ຍຸງ, ແມ່ກາຝາກ ແລະ ແມງໄມ້ ໃນແຂວງພາກໃຕ້ຂອງລາວ. ຂໍ້ມູນຈາກການເຝົ້າລະວັງພົບເຫັນການຕ້ານຕໍ່ຢາອາກເຕມີຊີນິນໃນລະດັບສູງຫລາຍ. ເຖິງວ່າ ພວກເຮົາຍັງບໍ່ທັນພົບເຫັນລັກສະນະການຕ້ານຕໍ່ຢາ piperaquine ແຕ່ວ່າການຕ້ານຕໍ່ຢາດັ່ງກ່າວແມ່ນພົບຢູ່ປະເທດເພື່ອນບ້ານ ໄທ ແລະ ກຳປູເຈຍ ມາຕັ້ງແຕ່ປີ 2015 ເປັນຕົ້ນມາແລ້ວ ເຊິ່ງສະແດງວ່າ ໂອກາດທີ່ຈະພົບການຕ້ານຢູ່ລາວໃນປະຈຸບັນກໍ່ມີຄືກັນ.

- ພວກເຮົາໄດ້ຈັດຕັ້ງປະຕິບັດໂຄງການທົດລອງກຳຈັດມາລາເຣຍຢູ່ແຂວງສະຫວັນນະເຂດ ຮ່ວມກັບສູນໄຂ້ຍຸງ, ແມ່ກາຝາກ ແລະ ແມງໄມ້ ແລະ ພົບວ່າ ການປຸກລະດົມຂົນຂວາຍໃຫ້ປະຊາຊົນເຂົ້າຮ່ວມໂຄງການແມ່ນມີຄວາມສຳຄັນທີ່ສຸດ ແລະ ຍັງພົບວ່າ ຄົນທີ່ຖືເຊື້ອມາລາເຣຍໂດຍບໍ່ມີອາການສະແດງອອກ ແມ່ນພົບໄດ້ຫລາຍເຊິ່ງເຂົາເຈົ້າອາດເປັນແຫລ່ງສິ່ງຕໍ່ພະຍາດທີ່ສຳຄັນ. ຜົນການທົດລອງເບື້ອງຕົ້ນພົບວ່າ ການຢາຢຢາ dihydroartemisinin-piperaquine ສົມທົບກັບຢາ primaquine ໃນປະລິມານຕ່ຳ ໃຫ້ກິນທົ່ວປວງຊົນ (MDA) ແມ່ນມີຄວາມເປັນໄປໄດ້, ເປັນທີ່ຍອມຮັບຂອງປະຊາຊົນ ແລະ ມີຄວາມປອດໄພສູງ, ແຕ່ຜົນກະທົບຂອງການກິນຢາຕໍ່ລະດັບການແຜ່ເຊື້ອ ຈະຕ້ອງໄດ້ສຶກສາຕື່ມອີກ.

- ປະຈຸບັນ ຍັງມີຄວາມກັງວົນກ່ຽວກັບການແຜ່ກະຈາຍຂອງເຊື້ອຟານຊີປາຣອມທີ່ຕ້ານຕໍ່ຢາ ອາກເຕມີຊີນິນ ຢູ່ທາງພາກໃຕ້ຂອງລາວ ແລະ ມີຄວາມຈຳເປັນຈະຕ້ອງໄດ້ຫາລືກັນວ່າ ເຮົາຈະໃຊ້ຢາປິ່ນປົວຊະນິດໃດ ຖ້າຢາປະສົມ ACTs ສອງຕົວຫາກໃຊ້ບໍ່ໄດ້ຜົນແລ້ວ. ສະນັ້ນ ພວກເຮົາກຳລັງຮ່ວມມືກັບສູນໄຂ້ຍຸງ, ແມ່ກາຝາກ ແລະ ແມງໄມ້ ເຮັດການຄົ້ນຄວ້າແບບຫລາຍສູນ (TRAC-2) ເພື່ອສຶກສາການຕ້ານຂອງເຊື້ອຟານຊີປາຣອມຕໍ່ຢາອາກເຕມີຊີນິນ ຢູ່ທີ່ໂຮງໝໍແຂວງເຊກອງ ໂດຍແມ່ນໜ່ວຍງານຄົ້ນຄວ້າ MORU ຢູ່ບາງກອກເປັນຜູ້ປະສານງານ. ການສຶກສານີ້ ເປັນໃນຮູບແບບການທົດລອງທາງ

ຄລີນິກແບບຊຸ່ມ ເພື່ອປຽບທຽບໄລຍະເວລາທີ່ເຊື້ອໝົດໄປຈາກກະແສເລືອດ ລະຫວ່າງຢາ artemether-lumefantrine ແລະ artemether-lumefantrine plus amodiaquine. ພວກເຮົາຄາດວ່າ ຂໍ້ມູນທີ່ໄດ້ຈາກການສຶກສານີ້ ຈະເປັນປະໂຫຍດສຳລັບການວາງແນວທາງນະໂຍບາຍປິ່ນປົວ ພະຍາດໄຂ້ມາລາເຣຍ ຂອງ ສປປ ລາວ ໃນຕໍ່ໜ້າ.

- ການບ່ຽງມະຕິໄຂ້ມາລາເຣຍແບບໄວອາ. ພວກເຮົາໄດ້ປະເມີນຄວາມສາມາດຂອງພະນັກງານແພດ ໃນການນຳໃຊ້ຊຸດກວດສອບຄຸນນະພາບຂອງແຜ່ນຈຸ່ມກວດໄຂ້ມາລາເຣຍ - ເຊິ່ງຖືການນຳໃຊ້ຢ່າງແຜ່ຫລາຍເພື່ອບ່ຽງມະຕິພະຍາດດັ່ງກ່າວໃນ ສປປ ລາວ (ທີ່ອາດເຊື່ອມຄຸນນະພາບ ເວລາຢູ່ໃນສະພາບອາກາດຮ້ອນ). ເຄື່ອງກວດສອບຄຸນນະພາບດັ່ງກ່າວເອີ້ນວ່າ positive control wells (PCW) ເຊິ່ງສາມາດກວດສອບແຜ່ນຈຸ່ມທີ່ເຊື່ອມຄຸນນະພາບ. ພາຍຫລັງການອົບຮົມວິທີນຳໃຊ້ ຊຸດກວດສອບຄຸນນະພາບດັ່ງກ່າວ, ຜູ້ເຂົ້າຮ່ວມການອົບຮົມສ່ວນໃຫ່ຍສາມາດເຮັດການກວດສອບ 6 ຂັ້ນຕອນຫລັກ ໄດ້ຢ່າງຖືກຕ້ອງ ແລະ ປະມານ 97% ຂອງຜູ້ເຂົ້າຮ່ວມ ສາມາດບອກແນວທາງທີ່ຈະຕ້ອງປະຕິ ບັດສຳລັບການນຳໃຊ້ຊຸດກວດສອບຄຸນນະພາບໃນພາກສະໜາມໄດ້ຢ່າງຖືກຕ້ອງ. ຊຸດກວດສອບຄຸນນະພາບດັ່ງກ່າວ ຈະເຮັດໃຫ້ພະນັກງານແພດມີຄວາມໝັ້ນໃຈໃນຜົນກວດໄຂ້ມາລາເຣຍຫລາຍຂຶ້ນກວ່າເກົ່າ ເຊິ່ງຈະສົ່ງຜົນດີໃຫ້ແກ່ໂຄງການຄວບຄຸມພະຍາດໄຂ້ມາລາເຣຍ. ຂໍ້ມູນຈາກການສຶກສາຄັ້ງນີ້ ຊີ້ໃຫ້ເຫັນວ່າ ເຮົາສາມາດເອົາຊຸດກວດສອບຄຸນນະພາບ ມານຳໃຊ້ເພື່ອກວດສອບຄຸນນະພາບຂອງແຜ່ນຈຸ່ມໄຂ້ມາລາເຣຍໄດ້.

* ສາເຫດ ແລະ ການປິ່ນປົວໄຂ້ ໃນເຂດຊົນນະບົດຂອງ ສປປ ລາວ.

- ພາຍໄຕ້ການສະໜັບສະໜູນຂອງ US Naval Medical Research Centre-Asia ພວກເຮົາໄດ້ຂະຫຍາຍໂຄງການຄົ້ນຄວ້າຫາສາເຫດຂອງໄຂ້ ໃນຄົນເຈັບເຂດນອກ ຂອງໂຮງໝໍແຂວງຊຽງຂວາງ, ສາລະວັນ ແລະ ຫລວງນ້ຳທາ. ສາເຫດຕົ້ນຕໍຂອງໄຂ້ທີ່ພົບໃນໄລຍະ 1 ປີ ໄດ້ແກ່: ພະຍາດໄຂ້ຫວັດ (60%), ໄຂ້ຍ່ຽວໜູ (15%), ໄຂ້ຍູງລາຍ (10%), Scrub typhus (5%), ຊຶມເຊື້ອເລືອດ (5%), murine typhus (3%), ອັກເສບສະໝອງຍີ່ປຸ່ນ (1%) ແລະ *Rickettsia* spp. (1%). ພະຍາດ Melioidosis ພົບເຫັນປະມານ 2.5% ໃນຄົນເຈັບແຂວງສາລະວັນ ແຕ່ບໍ່ພົບໃນແຂວງຫລວງນ້ຳທາເລີຍ. ພວກເຮົາໄດ້ດຳເນີນການສຶກສາໃນລັກສະນະນີ້ອີກໃນຄົນເຈັບນອນ ນັບແຕ່ເດືອນສິງຫາ 2017 ເປັນຕົ້ນມາ ແລະ ຄາດວ່າຜົນຈາກການຄົ້ນຄວ້ານີ້ ຈະມີຄວາມສຳຄັນສຳລັບການສົນທະນາເພື່ອວາງເປັນແນວທາງການປິ່ນປົວໃນອະນາຄົດ.
- ເມລິອອຍໂດຊິສ ເປັນສາເຫດທີ່ສຳຄັນຂອງການຊຶມເຊື້ອເລືອດທີ່ມັກຈະບໍ່ຄົ້ດຫາ ໃນ ສປປລາວ ແລະ ໃນຂົງເຂດປະເທດເຂດຮ້ອນ. ນັບແຕ່ປີ 1999 ມາຮອດປະຈຸບັນ ພວກເຮົາໄດ້ບ່ຽງມະຕິຄົນເຈັບເປັນພະຍາດເມລິອອຍ ຈຳນວນຫລາຍກວ່າ 1,234 ຄົນ (ສະເພາະໃນປີ 2017 ພົບ 144 ຄົນ) ແລະ ພວກເຮົາກັງວົນວ່າ ຍັງມີຄົນເຈັບພະຍາດດັ່ງກ່າວອີກຫລາຍໆຄົນທີ່ບ່ຽງມະຕິບໍ່ໄດ້ ແລະ ອາດເສຍຊີວິດຈາກການຕິດເຊື້ອພະຍາດດັ່ງກ່າວ ໂດຍສະເພາະໃນເຂດພາກໃຕ້ຂອງລາວ. ພວກເຮົາເຮັດການປະເມີນຊຸດການບ່ຽງມະຕິແບບໄວທີ່ໃຊ້ກັບຕົວຢ່າງຈາກຄົນເຈັບໂດຍກົງ ແລະ ຜົນເບື້ອງຕົ້ນພົບວ່າ ມັນມີຄວາມຈຳເພາະສູງ ແຕ່ຄວາມແມ່ນຍຳບໍ່ຄ່ອຍດີ. ພວກເຮົາຄາດວ່າ ຈະຈັດການສຳມະນາກ່ຽວກັບພະຍາດທີ່ສຳຄັນດັ່ງກ່າວໃນ ສປປ ລາວ ໃນປີ 2018 ຫລື 2019.
- ການບ່ຽງມະຕິພະຍາດໄຂ້ຍ່ຽວໜູ ຍັງມີຄວາມທ້າທາຍຫລາຍໃນຂົງເຂດອາຊີ ໂດຍສະເພາະໃນເຂດຊົນນະບົດຫ່າງໄກສອກຫລີກ. ຈາກການຄົ້ນຄວ້າໃນໂຮງໝໍມະໂຫສົດພວກເຮົາພົບວ່າ: ມາຮອດປະຈຸບັນ ແມ່ນຍັງບໍ່ທັນມີຊຸດການບ່ຽງມະຕິແບບໄວສຳລັບກວດຫາທາດກາຍຕ້ານຕໍ່ເຊື້ອ *Leptospira* spp. ທີ່

ມີຄວາມແມ່ນຍຳ ແລະ ຄວາມຈຳເພາະສູງ ເພື່ອຈະນຳມາໃຊ້ໄດ້ເທື່ອ. ແຕ່ມີເຮົາມີຂໍ້ມູນຊີ້ໃຫ້ເຫັນວ່າ ການກວດດ້ວຍເຕັກນິກທາງພັນທຸກຳ (PCR) ໃນຕົວຢ່າງນ້ຳຍ່ຽວ ແລະ ເຊຣອມຂອງຄົນເຈັບ ເປັນເຕັກນິກທີ່ມີປະໂຫຍດ ແຕ່ຍັງມີຄວາມຈຳເປັນຕ້ອງເຮັດການຄົ້ນຄວ້າຫາວິທີການກວດທີ່ມີລາຄາຖືກ ເຊິ່ງຈະສາມາດນຳໃຊ້ໃນລະດັບໂຮງໝໍແຂວງໄດ້.

- ໃນ ສປປ ລາວ ມີເຊື້ອພະຍາດຈັກຊະນິດ? ໃນ 15 ປີຜ່ານມາ ປະກົດວ່າໄດ້ມີຈຳນວນເຊື້ອພະຍາດທີ່ຖືກກວດພົບຫລາຍຂຶ້ນຢ່າງໄວວາ. ແລ້ວຍັງຈະຖືກຄົ້ນພົບອີກບໍ່? ພວກການຊອກຄົ້ນຫາໃນ ບົດຕີພິມເຜີຍແຜ່ແຕ່ປີ 1874 ຫາ ປີ 2016 ພົບວ່າ: ມີເຊື້ອພະຍາດໃນຄົນຈຳນວນ 159 ຊະນິດ ທີ່ຖືກບັນທຶກໃນ ສປປ ລາວ ບໍ່ວ່າຈະດ້ວຍເຕັກນິກການປູກເຊື້ອ ຫລື ເຕັກນິກທາງພັນທຸກຳ. ພວກຈາກການໃຊ້ mathematical model ແບບໃໝ່ໂດຍພິຈາລະນາອັດຕາການຄົ້ນພົບຕາມການເວລາ ໄດ້ຄາດຄະເນໄວ້ວ່າ: ໃນ ສປປ ລາວ ຍັງມີເຊື້ອພະຍາດຂອງຄົນປະມານ 10 - 11 ຊະນິດ ທີ່ຍັງຈະຕ້ອງໄດ້ຄົ້ນຫາຕື່ມອີກ.

- ສາເຫດຂອງການຊຶມເຊື້ອລະບົບປະສາດສູນກາງ ໃນຄົນເຈັບຈຳນວນ 1,065 ຄົນ ທີ່ໄດ້ຮັບການແທງນ້ຳໄຂສັນຫລັງໄປກວດ ທີ່ໂຮງໝໍມະໂຫສົດ ຊ່ວງປີ 2003-2011 ກຳລັງຖືກວິເຄາະຂໍ້ມູນ. ປະມານ 42% ຂອງຄົນເຈັບ ແມ່ນຮູ້ສາເຫດຈາກການກວດນ້ຳໄຂສັນຫລັງ ແລະ ຈາກການ ກວດເລືອດ. ໃນຈຳນວນຄົນເຈັບທີ່ຕິດເຊື້ອພຽງຊະນິດດຽວ, ສາເຫດທີ່ພົບຫລາຍກວ່າໝູ່ແມ່ນ ອັກເສບສະໝອງຍີ່ປຸ່ນ (8.8%), *Cryptococcus* spp. (6.6%), *Orientia tsutsugamushi* (2.9%), Dengue virus (2.5%), *Leptospira* spp. (2.3%), *Rickettsia* spp. (2.3%), *Streptococcus pneumoniae* (2.1%), *Mycobacterium tuberculosis* (1.9%), *Herpes simplex virus* (HSV) (1.4%), *Cytomegalovirus* (CMV) 12 (1.1%), *Enterovirus* (0.9%), *Varicellazoster virus* (VZV) (0.6%), *Mumps virus* (0.5%) and *P. falciparum* (0.4%). ອັດຕາການຕາຍແມ່ນສູງເຖິງ 26.3%. ຄົນເຈັບທີ່ຕິດເຊື້ອໄວຣັສມັກຈະມີອາການຄໍແຂງຫລາຍກວ່າກຸ່ມທີ່ບໍ່ຕິດເຊື້ອໄວຣັສ, ສ່ວນຄົນເຈັບທີ່ຕິດເຊື້ອຈຸລິນຊີມັກຈະມີປະຫວັດເປັນເບົາຫວານຫລາຍກວ່າກຸ່ມຄົນທີ່ບໍ່ຕິດເຊື້ອຈຸລິນຊີ. ປັດໄຈທີ່ພົວພັນກັບສາເຫດການຕາຍຢ່າງມີຄວາມສຳຄັນດ້ານສະຖິຕິໄດ້ແກ່ ການທີ່ມີລະດັບ Lactate ສູງໃນນ້ຳໄຂສັນຫລັງ ແລະ ຄະແນນ GCS ຕ່ຳ. ຂໍ້ມູນນີ້ ຊີ້ໃຫ້ເຫັນວ່າ: ເຮົາຕ້ອງເອົາໃຈໃສ່ເປັນພິເສດຕໍ່ຄົນເຈັບທີ່ມີຄະແນນ GCS ຕ່ຳ ເຊິ່ງຄົນເຈັບກຸ່ມນີ້ມີແນວໂນ້ມທີ່ຈະເສຍຊີວິດສູງ - ສະນັ້ນ ການປິ່ນປົວປະຄັບປະຄອງຄົນເຈັບທີ່ສະຕິບໍ່ດີ ເຊັ່ນ ການຕິດຕາມໃນຫ້ອງມໍລະສຸມ ສົມທົບກັບການໃຫ້ຢາຕ້ານເຊື້ອທີ່ເໝາະສົມໃນທັນທີອາດເປັນແນວທາງຫລັກໃນການຫລຸດຜ່ອນອັດຕາການຕາຍລົງ. ເນື່ອງຈາກວ່າ ສາເຫດທີ່ເກີດຈາກການຕິດເຊື້ອຣິກເກັດເຊັຍຂ້ອນຂ້າງສູງ ສະນັ້ນ ຄວນພິຈາລະນາປິ່ນປົວດ້ວຍຢາຕ້ານເຊື້ອ Ceftriaxone + doxycycline ໃນຂະນະທີ່ລໍຖ້າຜົນກວດທາງຫ້ອງວິເຄາະ.

- ພວກເຮົາຍັງພົບວ່າ ສ່ວນໃຫ່ຍຂອງນ້ຳໄຂສັນຫລັງທີ່ສົ່ງກວດ (94%) ໃນນະຄອນຫລວງວຽງຈັນ ແມ່ນມີຄວາມຜິດປົກກະຕິ ເຊິ່ງຊີ້ໃຫ້ເຫັນວ່າ: ເຮົາຄວນເອົາໃຈໃສ່ໃຫ້ມີການເຈາະນ້ຳໄຂສັນຫລັງ ໃນຄົນເຈັບທີ່ສົງໃສວ່າມີການຊຶມເຊື້ອລະບົບປະສາດສູນກາງທຸກກໍລະນີ ເພື່ອຫລີກເວັ້ນການພາດໂອກາດປິ່ນປົວຄົນເຈັບດັ່ງກ່າວ.

- ພວກເຮົາກຳລັງວິເຄາະຜົນຈາກການສຶກສາຄົ້ນຄວ້າຂະໜາດໃຫ່ຍ ເພື່ອຫາສາເຫດ ແລະ ຜົນກະທົບຂອງໄຂ້ໃນແມ່ຍິງຖືພາ ທີ່ເມືອງປາກງື່ມ, ນະຄອນຫລວງວຽງຈັນ. ອັດຕາການຕາຍຂອງແມ່ທີ່ສູງ ໃນ ສປປ ລາວ (ສູງກວ່າໝູ່ໃນອາຊີຕາເວັນອອກຊ່ຽງໄຕ້) ເຮັດໃຫ້ພວກເຮົາເຮັດການສຶກສາຄັ້ງນີ້. ໃນຈຳນວນແມ່ມານ 1,000 ຄົນ ທີ່ເຮັດການສຶກສາ, ມີ 110 ຄົນ ທີ່ມີອາການໄຂ້ໃນລະຫວ່າງຖືພາ ຫລື ຫລັງເກີດລູກ. ໃນຈຳນວນນີ້ 18 ຄົນ ລູລູກ, ເດັກຕາຍຮອບເກີດມີ 6 ຄົນ, 3 ຄົນ ຕາຍຫລັງເກີດມາ

ໃໝ່ໆ, ແມ່ 1 ຄົນເສຍຊີວິດ (ຍ້ອນຖືພາລູກນອກທ້ອງ) ແລະ ມີເດັກຈຳນວນ 11 ຄົນ ທີ່ເກີດມາຜິດປົກກະຕິ. ປະຈຸບັນ ພວກເຮົາກຳລັງວິເຄາະຫາສາເຫດຂອງໄຂ້ ແລະ ຫາຄວາມສຳພັນລະຫວ່າງອາການໄຂ້ ກັບພາວະອື່ນໆ ເຊັ່ນ ນ້ຳໜັກເກີດຕ່ຳ ແລະ ເດັກເກີດມາເສຍຊີວິດ.

- ຜົນການສຶກສາທົດລອງທາງຄລີນິກສຳລັບການປິ່ນປົວພະຍາດໄຂ້ໝັດໝູ (Murine typhus – ທີ່ເກີດຈາກເຊື້ອ *Rickettsia typhi*) ຢູ່ທີ່ໂຮງໝໍມະໂຫສົດ ຊີ້ໃຫ້ເຫັນວ່າ ພວກເຮົາບໍ່ຄວນນຳໃຊ້ຢາ Azithromycin ເພື່ອປິ່ນປົວພະຍາດດັ່ງກ່າວ ແລະ ຄວນໃຊ້ Doxycycline 3 ຫລື 7 ມື້ ເຊິ່ງມີປະສິດທິພາບບໍ່ຕ່າງກັນ.
- ລະບາດວິທະຍາທາງດ້ານ Serotype ຂອງໄຂ້ຍູງລາຍແມ່ນມີຄວາມສັບສົນ, ສະນັ້ນ ພວກເຮົາຈຶ່ງສະເໜີໃຫ້ສ້າງລະບົບແຜນທີ່ການກະຈາຍຂອງເຊື້ອພະຍາດລະດັບຊາດ ທີ່ທຸກຄົນສາມາດເຂົ້າເຖິງ ທັງນີ້ ກໍເພື່ອເຮັດໃຫ້ການຕິດຕາມ ແລະ ເຝົ້າລະວັງການລະບາດຂອງພະຍາດມີຄວາມສະດວກຂຶ້ນກວ່າເກົ່າ.
- ຜົນການປະເມີນຊຸດການກວດແບບໄວ ເພື່ອຊອກຫາທາດກາຍຕ້ານຕໍ່ເຊື້ອໄວຣັສອັກເສບສະໝອງຍີ່ປຸ່ນ ໃນນ້ຳໄຂສັນຫລັງ ແລະ ໃນເຊຣອມຂອງຄົນເຈັບ ຊີ້ໃຫ້ເຫັນວ່າ ຄວາມແມ່ນຍຳຂອງມັນຍັງຕ່ຳຫລາຍ ແລະ ບໍ່ສາມາດນຳໃຊ້ໄດ້ໃນ ສປປ ລາວ.
- ຂໍ້ມູນຈາກການສຶກສາຂອງພວກເຮົາທີ່ໂຮງໝໍມະໂຫສົດຊີ້ໃຫ້ເຫັນວ່າ ການຕິດເຊື້ອໄວຣັສ Human Respiratory Syncytial Virus (RSV) ແມ່ນພົບເຫັນໄດ້ຫລາຍໃນ ສປປ ລາວ ແລະ ມັກມີຄວາມສຳພັນກັບອັກເສບປອດໃນກຸ່ມເດັກອ່ອນທີ່ເຂົ້ານອນປິ່ນປົວໃນໂຮງໝໍ.

* ຄວາມສຳຄັນຂອງສຸຂະພາບໜຶ່ງດຽວ

- ຕະຫລາດໃນ ສປປ ລາວ ເປັນສູນລວມຂອງຄົນໃນສັງຄົມ ແຕ່ພວກເຮົາຍັງບໍ່ທັນມີຂໍ້ມູນກ່ຽວກັບຄວາມຮັບຮູ້ຂອງຜູ້ຄ້າຂາຍ ຕໍ່ກັບຄວາມສ່ຽງດ້ານສຸຂະພາບທີ່ອາດເກີດຈາກສິ່ງທີ່ເຂົາເຈົ້າຂາຍ. ເນື່ອງຈາກວ່າ ສັດປ່າ ແລະ ສັດບ້ານ ມີໂອກາດເປັນຕົວການນຳເຊື້ອພະຍາດມາສູ່ຄົນ, ສະນັ້ນ ພວກເຮົາຈຶ່ງໄດ້ເຮັດການຄົ້ນຄວ້າໃນຕະຫລາດກັບຊາວຄ້າຂາຍສັດປ່າ ແລະ ພົບວ່າ: ເກືອບທັງໝົດຂອງຜູ້ຄ້າຂາຍດັ່ງກ່າວ ແມ່ນມີຄວາມຮັບຮູ້ທີ່ຕ່ຳ ກ່ຽວກັບກັບຄວາມສ່ຽງຕໍ່ສຸຂະພາບຂອງເຈົ້າເຈົ້າ ໃນສິ່ງທີ່ເຂົາເຈົ້າຂາຍ. ຍັງມີຄວາມຈຳເປັນຕ້ອງເຮັດການຄົ້ນຄວ້າດ້ານສຸຂະພາບໜຶ່ງດຽວຕື່ມອີກ ເພື່ອໃຫ້ເຂົ້າໃຈກ່ຽວກັບຄວາມສ່ຽງ ແລະ ໃຫ້ໂຄສະນາສຸຂະສຶກສາແກ່ຊາວຄ້າຂາຍ ແລະ ຜູ້ທີ່ມາຊື້ສິນຄ້າ.
- ເຊື້ອພະຍາດໃນຊິ້ນສັດປ່າ. ການວິໄຈຕົວຢ່າງຊິ້ນສັດປ່າທາງພັນທຸກຳ ຈຳນວນ 717 ຕົວຢ່າງ ຈາກສັດປ່າທີ່ມີກະດູກສັນຫລັງ (ສ່ວນໃຫ່ຍແມ່ກະຮອກ-ກະແຕ) ຈຳນວນ 359 ໂຕ ທີ່ໄດ້ມາຈາກຕະຫລາດ ພົບວ່າ: ມີສັດຈຳນວນ 469 ໂຕ ທີ່ມີເຊື້ອ *Leptospira* spp., 19 ໂຕ ມີເຊື້ອ *Rickettsia* spp. (ລວມທັງເຊື້ອ *R. felis* 1 ເຊື້ອ). ການກວດພົບເຊື້ອ *Leptospira* spp. ໃນອັດຕາທີ່ສູງ ຈາກຕົວຢ່າງທີ່ຕ້ອຍມາຈາກທ່ຽງ-ອະໄວຍະວະເພດຂອງສັດ ຊີ້ໃຫ້ເຫັນເຖິງຄວາມເປັນໄປໄດ້ສຳລັບການສິ່ງຕໍ່ພະຍາດໄຂ້ຍ່ຽວໜູ ຈາກໂຕກະຮອກ-ກະແຕ ໄປສູ່ຄົນໃນຕະຫລາດ. ນອກນີ້ ພວກເຮົາຍັງກວດພົບບາງຕົວຢ່າງທີ່ມີເຊື້ອ *O. tsutsugamushi*, *L. garvieae*, *Kurthia* spp., *Ehrlichia* spp. TC251-2, *Anaplasma marginale*, *A. phagocytophilum*, and *A. bovis*. ຂໍ້ມູນນີ້ ສະໜັບສະໜູນຄວາມພະຍາຍາມທີ່ຈະຕ້ອງເອົາໃຈໃສ່ຄວບຄຸມການຄ້າຂາຍສັດປ່າຕື່ມອີກ.

- ການນຳໃຊ້ເຕັກນິກການບິ່ງມະຕິທາງພັນທຸກຳແບບໃໝ່ ສາມາດກວດພົບດີເອັນເອຂອງ ເຊື້ອ *Angiostrongylus cantonesis* ໃນນ້ຳໄຂສັນຫລັງຂອງຄົນເຈັບລາວທີ່ເປັນອັກເສບເຍື່ອຫຸ້ມສະໝອງ ຊະນິດ eosinophilic meningitis ເຊິ່ງປົກກະຕິຄົນເຮົາຈະຕິດພະຍາດນີ້ຈາກການກິນຫອຍ ຫລື ສັດນ້ຳ ທີ່ດິບ ຫລື ບໍ່ສຸກ. ຂໍ້ມູນດັ່ງກ່າວຊີ້ໃຫ້ເຫັນຄວາມສຳຄັນຂອງການໂຄສະນາສຸຂະສຶກສາ ໃຫ້ປະຊາຊົນຮັບຮູ້ໃນເລື່ອງຄວາມສ່ຽງສຳລັບອາຫານການກິນ.
- ນັບແຕ່ປີ 2000 ເປັນຕົ້ນມາ ທາງໂຄງການ LOMWRU ສາມາດຄົ້ນພົບເຊື້ອ *Streptococcus agalactiae* (Group B Streptococcus - GBS) ທີ່ມີລັກສະນະທາງພັນທຸກຳຄືກັບເຊື້ອທີ່ພົບເຫັນ ໃນລະຫວ່າງການລະບາດຂອງພະຍາດທີ່ເກີດຈາກປາທີ່ປະເທດສິງກະໂປໃນປີ 2015 (ST283) ເຊິ່ງ ພວກເຮົາກວດພົບໃນຄົນເຈັບຈຳນວນ 28 ຄົນ ຈາກທັງໝົດ 38 ກໍລະນີທີ່ມີການຊຶມເຊື້ອ GBS ຮຸນແຮງ. ເນື່ອງຈາກວ່າເຊື້ອສາຍພັນດັ່ງກ່າວພົບໃນຄົນທີ່ຕິດເຊື້ອ ແລະ ປາ ໃນຂົງເຂດອາຊີຕາເວັນອອກຊ່ຽງໄຕ້ ສະນັ້ນ ປາອາດເປັນແຫລ່ງຂອງພະຍາດທີ່ເກີດຈາກເຊື້ອ GBS ໃນຂົງເຂດນີ້ທີ່ເຮົາຍັງມອງຂ້າມຢູ່.
- ພະຍາດອ້ຍັງເປັນໄພຄຸກຄາມທີ່ສຳຄັນຕໍ່ສຸຂະພາບຂອງຄົນເຮົາ. ຈາກຕົວຢ່າງໝາຈຳນວນ 415 ຕົວຢ່າງ ທີ່ສົ່ງໄປກວດຢູ່ຫ້ອງວິເຄາະສັດຕະວະແພດແຫ່ງຊາດ ນັບແຕ່ປີ 2010 ເປັນຕົ້ນມາ, ໃນນີ້ 284 ຕົວຢ່າງ ທີ່ສົ່ງໄປກວດຢູ່ຫ້ອງວິເຄາະສັດຕະວະແພດແຫ່ງຊາດ ນັບແຕ່ປີ 2010 ເປັນຕົ້ນມາ, ໃນນີ້ 284 ຕົວຢ່າງແມ່ນພົບເຊື້ອພະຍາດອ້.

* ຄວາມສຳຄັນຂອງຄຸນນະພາບຢາ

- ບັນຫາຄຸນນະພາບຂອງຢາປິ່ນປົວຫລາຍຊະນິດ ຍັງເປັນເລື່ອງທີ່ໜ້າກັງວົນໃນທົ່ວໂລກ. ການສຶກສາ ຂອງພວກເຮົາພົບວ່າ ມີຢາ sofosbuvir ປອມ ທີ່ປະເທດພະມ້າ ເຊິ່ງອັນນີ້ເຮັດໃຫ້ເກີດມີຄວາມສ່ຽງ ຕໍ່ການປິ່ນປົວພະຍາດຕັບອັກເສບຊີໃນປະເທດເຮົາ ເພາະຢາດັ່ງກ່າວກຳມີຂາຍໃນ ສປປ ລາວ ເຊັ່ນກັນ. ນອກນີ້ ພວກເຮົາຍັງພົບວ່າ ການນຳໃຊ້ຢາ Artemisinin ຊະນິດດຽວ ເຂົ້າໃນການປິ່ນປົວມາລາເຣຍ ແລະ ຢາປະສົມ ACTs ທີ່ບໍ່ຮັບປະກັນຄຸນນະພາບ ຍັງເປັນບັນຫາທີ່ສຳຄັນໃນພາກພື້ນນີ້.
- ໂດຍການຮ່ວມມືກັບ ກອງກວດກາອາຫານ ແລະ ຢາ, ພວກເຮົາກຳລັງປະເມີນເຄື່ອງກວດຄຸນນະພາບ ຂອງຢາທີ່ສາມາດພົກພາໄປ-ມາໄດ້ ຫລາຍໆຍີ່ຫໍ້ ເບິ່ງວ່າມັນມີຄວາມແມ່ນຍຳຫລາຍໜ້ອຍປານໃດ ແລະ ຄຸ້ມຄ່າຫລາຍປານໃດ ໂດຍໄດ້ຮັບທຶນສະໜັບສະໜູນຈາກທະນະຄານພັດທະນາອາຊີ. ຜົນຈາກການປະເມີນຄັ້ງນີ້ ຈະຊ່ວຍໃຫ້ເຮົາຮູ້ວ່າ ເຄື່ອງຊະນິດໃດທີ່ຈະເໝາະສົມສຳລັບປະເທດເຮົາຫລາຍທີ່ສຸດ. ຈະມີກອງປະຊຸມຫາລືກ່ຽວກັບຜົນຈາກການປະເມີນນີ້ ທີ່ວຽງຈັນ ໃນລະຫວ່າງວັນທີ 9-10 ເມສາ 2018.
- ພວກເຮົາຄົ້ນພົບວ່າ ການນຳໃຊ້ຢາທີ່ບໍ່ມີສະຫລາກໃນນະຄອນຫລວງວຽງຈັນ ແມ່ນມີຄວາມສຳພັນກັບ ອັດຕາການເຂົ້ານອນໂຮງໝໍຍ້ອນກຳມະຜົນສຳຮອງຂອງຢາ ທີ່ກຳລັງເພີ່ມຂຶ້ນເລື້ອຍໆ ເຊິ່ງຂໍ້ມູນນີ້ ຊີ້ໃຫ້ເຫັນວ່າ ມັນມີຄວາມຈຳເປັນທີ່ຈະຕ້ອງເອົາໃຈໃສ່ກ່ຽວກັບວຽກງານການຕິດສະຫລາກໃສ່ຫໍ່ຢາ ໃນເວລາຈ່າຍຢາໃຫ້ຄົນເຈັບ.
- ການສຶກສາຂອງພວກເຮົາພົບວ່າ ປະຊາຊົນໃນນະຄອນຫລວງວຽງຈັນ ຍັງມີຄວາມຮັບຮູ້ທີ່ຈຳກັດ ໃນເລື່ອງຄວາມສ່ຽງຂອງຢາປິ່ນປົວ. ຂໍ້ມູນນີ້ ຊີ້ໃຫ້ເຫັນວ່າ ການປຸກລະດົມ ແລະ ໃຫ້ສຸຂະສຶກສາແກ່ປະຊາຊົນ ຈະເຮັດໃຫ້ການນຳໃຊ້ຢາມີລັກສະນະສົມເຫດສົມຜົນຫລາຍຂຶ້ນກວ່າເກົ່າ.

* ຄວາມສຳຄັນຂອງວຽກງານໂຄສະນາສຸຂະສຶກສາ

- Science Café. ປະຈຸບັນ ສປປ ລາວ ມີຂໍ້ມູນດ້ານສຸຂະພາບຫລາຍຂຶ້ນກວ່າເກົ່າ, ສະນັ້ນ ການເຜີຍແຜ່ຂໍ້ມູນດັ່ງກ່າວໃຫ້ແກ່ຜູ້ສ້າງນະໂຍບາຍ, ພະນັກງານສາທາລະນະສຸກ, ແລະ ປະຊາຊົນທົ່ວໄປ ຈຶ່ງມີຄວາມສຳຄັນເປັນຢ່າງຍິ່ງ. ພວກເຮົາໄດ້ຮ່ວມມືກັບ ມະຫາວິທະຍາໄລວິທະຍາສາດສຸຂະພາບ ຈັດການສົນທະນາ ທີ່ເອີ້ນວ່າ Science Café ເປັນຄັ້ງທຳອິດໃນ ສປປ ລາວ ແລະ ພວກເຮົາຄາດວ່າ ຈຸດເລີ່ມຕົ້ນນີ້ ຈະກາຍເປັນສິ່ງທີ່ຄວນເຮັດຢ່າງເປັນປະຈຳໃນອະນາຄົດ ໃນຮູບແບບຂອງການສົນທະນາໃນຫົວຂໍ້ວິທະຍາສາດ.
- ການເຜີຍແຜ່ຜົນການຄົ້ນຄວ້າໃຫ້ຜູ້ຮັບຜິດຊອບນະໂຍບາຍສາທາລະນະສຸກ. ພວກເຮົາໄດ້ຈັດກອງປະຊຸມເຜີຍແຜ່ຜົນຂອງການຄົ້ນຄວ້າຈາກໂຄງການຂອງພວກເຮົາໃນປີ 2017 ທີ່ຜ່ານມາ ໃຫ້ທາງກົມຄວບຄຸມພະຍາດຕິດຕໍ່ ແລະ ກົມກອງ-ພາກສ່ວນອື່ນໆ ອ້ອມຂ້າງກະຊວງສາທາລະນະສຸກ ໄດ້ຮັບຊາບ ໃນຄັ້ງວັນທີ 8 ກຸມພາ 2018 ພ້ອມທັງໄດ້ນຳສະເໜີຄວາມໝາຍ-ຄວາມສຳຄັນ ຂອງຜົນການຄົ້ນຄວ້າຕໍ່ກັບນະໂຍບາຍດ້ານສາທາລະນະສຸກໃນ ສປປ ລາວ.

SUMMARY

Her Excellency Madame Claudine Ledoux, Ambassador of France, His Excellency Mr Hugh Evans, Ambassador of the UK with His Excellency the Minister of Health – Lao PDR- Professor Dr Bounkong Syhavong discussing in the Microbiology Laboratory

A. The Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit (LOMWRU) is a clinical research unit embedded within the Microbiology Laboratory of Mahosot Hospital. It was founded in 2000 as a part of the MORU Tropical Network and is strongly linked to MORU-Bangkok with which 41% of our studies are shared.

B. LOMWRU is core funded by the Wellcome Trust of Great Britain, with significant additional support from the US Naval Medical Research Centre, the Bill & Melinda Gates Foundation, the European Union, Department for International Development-UK (DFID), New Zealand e-Asia, Fondation Total/Institute Pasteur, Global Good, DTRA, Global Antibiotic Research Partnership, and the Asian Development Bank. Considerable assistance in kind is given by the Institut de Recherche pour le Développement/Aix-Marseille University, France, and the Rickettsial Diseases Research Program, Naval Medical Research Center, USA.

C. The Microbiology Laboratory, including LOMWRU, is composed of 29 Lao Government staff and 49 project-funded staff; 88% are Lao and 56% are female. The Microbiology Laboratory has clinical microbiology, molecular, serology and BSL3 laboratories. It follows University of Oxford safety policies and guidelines.

D. LOMWRU supports the infectious disease diagnostic service of Mahosot Hospital, assists provincial hospitals in Luang Nam Tha, Salavan and Xieng Khouang Provinces, performs clinical research and builds diagnostic and research human capacity through training and active participation. LOMWRU also works with the Centre for Malariology, Parasitology and Entomology on malaria projects in the five southern provinces, with the Lao Food and Drug Department (FDD), Bureau of Food and Drug Inspections (BFDI) and the Food & Drug Quality Control Centre (FDQCC) on the quality of medicines and with the Lao Ministry of Health DCDC (Department of Communicable Disease Control) on antibiotic resistance.

E. The main current focus of the research work is on the causes of fever and their epidemiology, their antimicrobial resistance patterns, their optimal diagnosis and optimum treatment, to inform policy in rural Asia and the quality of medicines globally.

Meeting in February 2018 with Dr Rattanaxay Phetsouvanh, Director of Department of Communicable Disease Control and key health workers from Ministry of Health to discuss LOMWRU health research activities in 2017

F. In 2017 we supported 12 Lao staff to attend 6 international meetings and short courses and supported three Lao staff to read for PhD/MSc degrees at Mahidol University, one at the University of Amsterdam and one to read the BSc in Medical Technology at Khon Kaen University.

G. In 2017 we published or have in press 43 publications, including 39 peer-reviewed papers, one letter and three book chapters. Since LOMWRU was founded, its staff has published 333 papers and book chapters.

H. Previous LOMWRU research translated into policy in Laos includes the implementation of vaccination against the pneumococcus and the *Japanese encephalitis virus* (JEV) and the change in national antimalarial and typhoid treatment policies. It also demonstrated the presence of numerous important pathogens for the first time in Laos, and highlighted the global importance of scrub typhus, leptospirosis, typhoid, melioidosis and JEV, providing evidence on their epidemiology and prompting interventions.

I. The main findings, in brief, from work published, in press or in preparation in 2017 of immediate relevance to Laos (please see caveats in the text), are:

- **Antimicrobial resistance (AMR) is, as elsewhere in the world, increasingly becoming a cause of significant concern for Lao public health.**

❖ Extended spectrum beta-lactamase producing, multi-drug resistant Enterobacteriaceae (ESBL) are increasingly important causes of infection in Mahosot Hospital. This is the commonest AMR problem the Microbiology Laboratory encounters, their hospital incidence is increasing and they are resistant to commonly used antibiotics such as cephalosporins and penicillins, and frequently to others such as gentamicin and ciprofloxacin/ofloxacin. We see isolates from patients with susceptibility profiles that indicate extremely limited options for therapy and we are greatly concerned that soon we will commonly see untreatable infections and infections that will require unaffordable antibiotics.

❖ ESBL-producing bacteria are also surprisingly common in the intestines of healthy people and animals in a remote village of Xieng Khouang Province, suggesting that ESBL are a problem in rural Laos and will become a greater problem unless action is taken. A surprisingly high proportion (13.4%) of the human population of the village

had taken antibiotics in the preceding 2 weeks.

- In addition, we found that overseas visitors attending a medical course in Vientiane, who provided their stools for analysis on arrival, rapidly acquired cephalosporin resistant bacteria in their stools during three weeks in Vientiane. These data suggest that ESBL bacteria are abundant in people and the environment in Vientiane and that those visiting rapidly become colonised, risking their health and the dissemination of these bacteria elsewhere.

- We have found the first isolates of carbapenem resistant Enterobacteriaceae in Laos, all *E. coli*, one from pus, one from the urinary tract and one causing bacteraemia (see cover photograph). In addition, carbapenem-resistant Acinetobacters are seen regularly in respiratory tract samples from the Intensive Care Unit at Mahosot Hospital. With the recent beginning of use of carbapenems in Laos, this is extremely worrying and calls for increasing oversight of their use to reduce the risk of increase in these extremely difficult to treat bacteria.

- The main causes of non-typhoid Salmonella bacteraemia at Mahosot Hospital are *S.* Enteritidis, *S.* Typhimurium and *S.* Choleraesuis. The majority of bloodstream isolates are non-susceptible to ciprofloxacin. A greater diversity was found in diarrhoeal stools, mainly *S.* Typhimurium, *S.* Weltevreden, and *S.* Stanley.

- Of 96 *Staphyococcus aureus* isolates, antibiotic resistance was uncommon except for penicillin (97%) and tetracycline (50%). Seven (7%) isolates were methicillin-resistant *S. aureus* (MRSA). MRSA seem to be increasing and are also of considerable concern as they are difficult to treat. *S. argenteus* was identified for the first time in Laos.

- Reinforcing the evidence that enhancing antibiotic stewardship and infection control practices is urgently needed, we have found *Clostridium difficile* in the stools of patients at Mahosot Hospital. The occurrence of this organism, an important cause of hospital-associated diarrhoea, is not unexpected considering the frequent cephalosporin use in

Dr Olivo Miotto and Assoc Prof Mayfong Mayxay speaking at Malaria Molecular Marker Meeting in Savannakhet 2017

Vientiane hospitals.

- Of 158 *N. gonorrhoeae* isolates with antibiotic susceptibility data, all were susceptible to ceftriaxone and spectinomycin, but with very high levels of resistance to ciprofloxacin, penicillin and tetracycline. These data suggest that ceftriaxone and spectinomycin are likely to be efficacious against *N. gonorrhoeae* in Laos. Contact tracing and treatment of partners will be key interventions to reduce the burden of sexually transmitted diseases.

- We are conducting a Global Point Prevalence Survey of Antimicrobial Consumption and Resistance (PPS) at four hospitals in Laos. We hope that these data will be very helpful for the Lao Ministry of Health, as the first estimates of hospital inpatient antibiotic use in Laos and to monitor changes and use the data to inform optimal prescribing policy.

- The spread of bacteria resistant to common antibiotics in Laos will have many deleterious consequences for patients, the community and the economy, and greater emphasis on infection control, antibiotic stewardship and regulation are urgently needed.

- To assist with providing an evidence base for appropriate action/intervention, we have joined with the Ministry of Health and key stakeholders, especially the Global Antibiotic Resistance Partnership, to form an AMR Technical Working Group that will be synergistic with the WHO/FAO/OIE AMR committee. We plan that this Group will meet in April 2018 to discuss the results of the Lao GARP-AMR review.

- We are working on a tabulation and mapping system for the quality of antibiotics globally, that will help inform discussions and modelling of the

Stata training course led by Khun Atthanee Jeeyapant April 2017

Boat at sunset on the River Mekong

relationship between medicine quality and AMR

- **Malaria and the Importance of Elimination for Laos**

❖ We are continuing malaria molecular marker surveillance, with CMPE, in southern Laos. This demonstrates very high frequencies of falciparum malaria markers of artemisinin resistance. Markers of piperaquine resistance have not yet been found in Laos, but these have been present in Thailand and Cambodia since 2015, suggesting that parasites with these markers are likely now to be in Laos.

❖ We have conducted a large Targeted Malaria Elimination trial in Savannakhet Province, with CMPE, that has demonstrated the importance of targeted public engagement and that asymptomatic malaria is very common and probably facilitates malaria transmission. The preliminary results suggest that the mass drug administration (MDA) of dihydroartemisinin-piperaquine plus a single low dose of primaquine is feasible, acceptable and safe but its impact on malaria transmission needs to be further investigated.

❖ There remain serious concerns about the spread of artemisinin resistant *P. falciparum* parasites in southern Laos and discussions are needed as to what therapy will be recommended if double-therapy ACTs fails. We have been participating in the multicentre TRAC-2 study, with CMPE and coordinated by MORU-Bangkok, at Sekong Provincial Hospital. This is a randomised clinical trial comparing parasite clearance times between artemether-lumefantrine and artemether-lumefantrine plus amodiaquine. We hope that these data will be useful for informing optimal future national ACT policy.

❖ Malaria Rapid Diagnostic Tests (RDTs). We assessed health workers' (HW) ability to use a potential improvement on malaria RDTs, the mainstay of malaria diagnosis in Laos, which may become degraded in hot climates. The improvement includes positive control wells (PCW) to detect degraded RDTs. After training,

most participants correctly performed the six key individual PCW steps and 97% reported a correct action based on PCW use at routine work sites. PCW availability can improve HWs' confidence in RDT results, and benefit malaria diagnostic programs. These data support the implementation of PCWs in malaria RDTs.

▪ The causes and treatment of fevers in rural Laos

❖ The Expanded Fever Surveillance (EFS) project, with the support of the US Naval Medical Research Centre-Asia, investigated the aetiology of fever in outpatients attending Xieng Khouang, Salavan and Luang Nam Tha Provincial Hospitals. The main diagnoses over one year were influenza (60%), followed by leptospirosis (15%), dengue (10%), scrub typhus and bacteraemia (both 5%), murine typhus (3%), JEV and *Rickettsia* spp. (both 1%). Melioidosis was found in 2.5% of patients in Salavan but in none in Xieng Khouang and Luang Nam Tha. This surveillance restarted in August 2017 for inpatients, and these data will be vital for informing treatment algorithm discussions.

❖ Melioidosis is an important and under-recognised cause of sepsis in Laos, as well as other tropical regions. We have diagnosed over 1,234 culture-positive patients since 1999 (144 in 2017 alone) and are concerned that there is substantial unrecognised but potentially treatable mortality due to *B. pseudomallei* elsewhere, especially in southern Laos. A rapid diagnostic test that can be performed directly on clinical samples has shown good specificity but only moderate sensitivity in preliminary evaluations. We hope to organise a workshop on this important pathogen in Laos in 2018 or 2019.

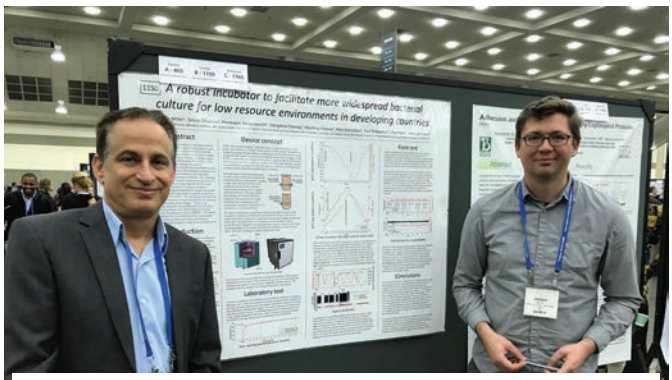
❖ The diagnosis of leptospirosis remains challenging in rural Asia. Data from a diagnostic evaluation at Mahosot Hospital suggest that there are no anti-*Leptospira* spp. antibody detecting RDTs with good sensitivity and specificity for local use. However, data suggest that PCR of urine and serum is a useful technique, but that more research on low-

Collaborative Institutional Training Initiative (CITI) Training of Microbiology Laboratory team by Ms Sophea Sout

cost PCR systems at the provincial level is needed.

❖ How many human pathogens are there in Laos? There has been a rapid increase in the number of pathogens described in Laos over the last ~ 15 years. Are there more to find? Searches of publications from 1874 to 2016 yielded evidence that 159 human pathogens have been recorded in Laos by culture and molecular assays. A novel mathematical model, incorporating a time-varying discovery rate, estimated that some further 10-11 species of human pathogens are currently waiting to be discovered in Laos.

❖ The causes of central nervous system infections for the first 1,065 lumbar punctures at Mahosot Hospital, 2003-2011, have been analysed. Aetiology, based on assays from blood and CSF, was confirmed in 42% patients. Among single infections, the most frequent aetiologies were the *Japanese encephalitis virus* (JEV) (8.8%), *Cryptococcus* spp. (6.6%), *Orientia tsutsugamushi* (2.9%), *Dengue virus* (2.5%), *Leptospira* spp. (2.3%), *Rickettsia* spp. (2.3%), *Streptococcus pneumoniae* (2.1%), *Mycobacterium tuberculosis* (1.9%), *Herpes simplex virus* (HSV) (1.4%), *Cytomegalovirus* (CMV) 12 (1.1%), *Enterovirus* (0.9%), *Varicella-zoster virus* (VZV) (0.6%), *Mumps virus* (0.5%) and *P. falciparum* (0.4%). The mortality was high at 26.3%. Patients with viral infection more frequently had neck stiffness than those without. Patients with bacterial infection were more likely to have a history of diabetes than those without. Factors that showed strong association with death were higher CSF lactate and lower GCS. The Lao data suggest that particular attention should be paid to patients presenting with decreased GCS and the provision of supportive care for unconscious patients, such as high-dependency units (HDU), along with appropriate urgent antimicrobial therapy may



Dr Michael Friend & Dr Andrew Miller, of Global Good, with their poster at ASTMH, Baltimore, November 2017

be key factors in improving outcome. Given the high frequency of rickettsial infections, empirical therapy with ceftriaxone plus doxycycline should be considered.

❖ The majority of laboratory cerebrospinal fluid examinations (94%) in Vientiane are abnormal, suggesting that lumbar punctures in inpatients with suspected central nervous system (CNS) infections should be facilitated, with a lower threshold for performing lumbar puncture, to ensure that patients with these infections are not missed.

❖ A large pilot cohort study of the causes and impact of fevers in pregnancy in Pak Gnum District, Vientiane is being analysed. Laos has the highest estimated maternal mortality in SE Asia and this prompted this large pilot study. Of 1,000 pregnant patients recruited, 110 developed intra- or post-partum fevers. There were 18 miscarriages, 6 perinatal deaths, 3 neonatal deaths, 1 maternal death (ectopic pregnancy) and 11 congenital abnormalities. The final diagnostic assays are being conducted before final analysis in relation to outcome measures such as low birth weight and stillbirth.

❖ A clinical trial of the treatment of uncomplicated murine typhus (*Rickettsia typhi*) at Mahosot Hospital suggests that oral azithromycin should not be used for therapy but that three and seven

days oral doxycycline have similar efficacy.

- The serotype epidemiology of dengue, and changes through time and space, is very complicated and we suggest a national mapping and accessible dashboard system to facilitate monitoring and warn of impending outbreaks.

- An evaluation of rapid diagnostic tests for anti-*Japanese encephalitis virus* antibodies in CSF and serum suggests that their diagnostic accuracy is too low for use in Laos.

- Data from Mahosot Hospital suggest that Human Respiratory Syncytial Virus (RSV) infection is frequent in Laos and commonly associated with pneumonia in hospitalized young children

The Importance of One Health

- Lao markets are fulcrums of society but there is no information on vendors' perception of health risk due to the food they sell. As wild and domestic animals are potential carriers of diverse diseases, we conducted a descriptive cross-sectional study in markets with traders selling wildlife. Nearly all vendors had a very low perception of risk for health from the food sold. Further One Health research is needed to understand risks and engage with the market communities, both buyers and sellers.

- Pathogens in bushmeat. Molecular assays on 717 specimens from 359 wild vertebrates (mostly squirrels) collected at markets demonstrated that 69 animals contained *Leptospira* spp. and 19 contained *Rickettsia* spp. (including a confirmed *R. felis*). The high frequency of *Leptospira* spp. detected in urogenital swabs suggests a potential risk of squirrel-human transmission of leptospirosis in markets. We also identified samples containing *O. tsutsugamushi*, *L. garvieae*, *Kurthia* spp., *Ehrlichia* spp. TC251-2, *Anaplasma marginale*, *A. phagocytophilum*, and *A. bovis*. These data support the public heath interest in controlling the commercial trade in bushmeat.

- Using a new PCR assay we have demonstrated DNA of *Angiostrongylus cantonensis*, which is usually acquired from eating raw or undercooked snails or other aquatic creatures, in the CSF of four Lao patients with eosinophilic meningitis, suggesting the need for public engagement over risky dietary practices.

- *Streptococcus agalactiae* (Group B Streptococcus - GBS) with the same sequence type as that which caused a unique fish-borne outbreak in Singapore in 2015 (ST283) accounted for 28 of 38 cases of invasive GBS infection diagnosed in LOMWRU since 2000. As this sequence type has been found in both human infections and fish in other countries in SE Asia, it is possible that fish may represent an under-recognised source of GBS infection regionally.

- Rabies remains a significant health hazard with 415 dog samples submitted to NAHL since 2010 for diagnosis – of these 284 were rabies-positive.

The Importance of Medicine Quality

- There remain severe, focal, problems with the quality of diverse medicines globally. Falsified sofosbuvir has been found in Myanmar and this is a risk for Lao Hepatitis C care as sofosbuvir is now available in Laos. There remain significant regional issues with the availability of oral artemisinin derivative monotherapy and non-Quality Assured ACTs.

- We are evaluating, with the Bureau of Food and

Drug Inspection, a wide diversity of portable medicine screening devices, their diagnostic accuracy and cost-effectiveness, funded by ADB. The results should help inform policy for which devices are best for Laos. A meeting to discuss these results will be held in Vientiane on 9-10th April 2018.

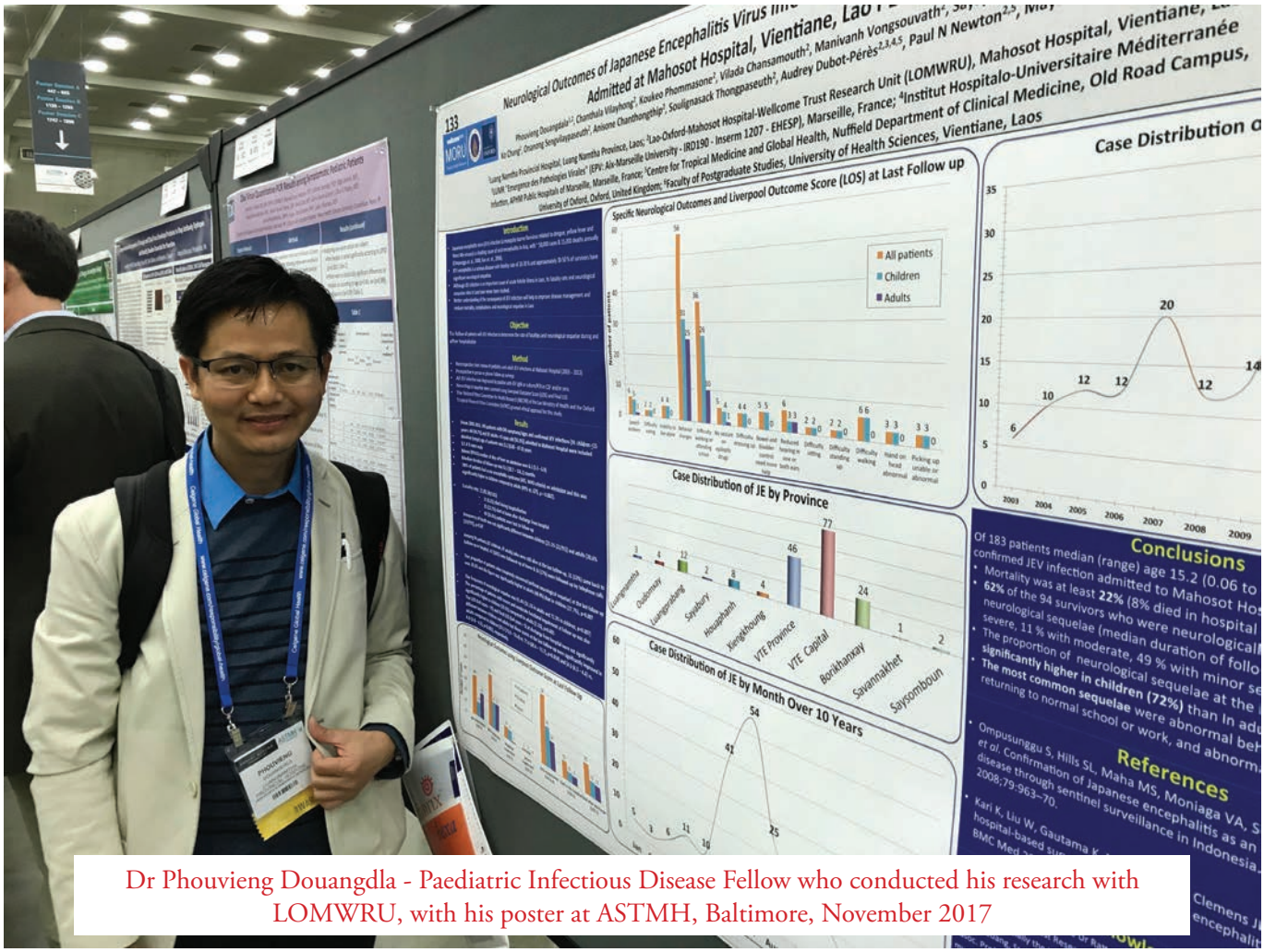
- The use of medicines without labelling in Vientiane is associated with increased frequency of admission to hospital with adverse drug reactions, suggesting that there is a need to ensure appropriate labelling of medicines at dispensing.

- There is limited awareness in Vientiane residents of the risks of medicines and more engagement with the public would make a valuable contribution to the appropriate use of medicines.

The Importance of Engagement

- Science Café. Now that there is more Lao public health information available, engagement with policy makers, health workers and the public is vital. With the University of Health Sciences we organised further Science Cafés in Laos, which we hope will become a regular feature of the Vientiane scientific 'scene'.

- Policy maker engagement. We met with the Department of Communicable Disease Control and other departments of the Lao Ministry of Health on February 8th 2018 to discuss our work in 2017 and the public health policy implications.



Dr Phouvieng Douangdla - Paediatric Infectious Disease Fellow who conducted his research with LOMWRU, with his poster at ASTMH, Baltimore, November 2017

INTRODUCTION

Rickettsial Coordination Meeting Vientiane March 2017

The Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit (LOMWRU) is a clinical research unit embedded within the Microbiology Laboratory of Mahosot Hospital, a Lao Government primary-tertiary hospital in Vientiane. LOMWRU core funding is from the Wellcome Trust of Great Britain, a charity now named 'Wellcome', through the University of Oxford. LOMWRU was founded in 2000 and is guided by a Memorandum of Understanding between Mahosot Hospital of the Lao Ministry of Health, the Wellcome Trust and the University of Oxford (2012-2022). It is housed in two buildings. The old Microbiology Laboratory (from the 1920s) houses the clinical microbiology laboratory, offices, administration and the medicine quality project, and was extended to create a modern microbiology laboratory in 2011 with funding from the University of Oxford. The upper floor of the Infectious Disease Centre (construction of the building was funded by the Wellcome Trust and opened in 2008) contains the Molecular, Serology and BSL3 Laboratories and offices.

The roof of the old Microbiology Laboratory has deteriorated over the last few years and with funding from the Wellcome Trust the roof was replaced and the building renovated in 2016/17. A reopening ceremony was performed by the Minister of Health, H.E. Professor Dr Bounkong Syhavong in May 2017 in the presence of the Ambassadors of the United Kingdom, France and the European Union.

The Chinese Government is funding the rebuilding of Mahosot Hospital and we expect that the Microbiology Laboratory, including LOMWRU, will move to a new Infectious Disease Centre later in 2018 or 2019.

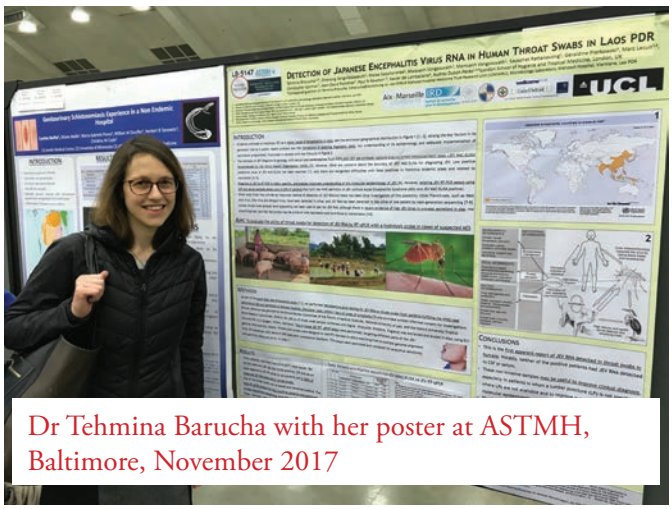
Our Oxford University headquarters are at the Centre for Tropical Medicine & Global Health, in the Nuffield Department of Medicine on the Churchill Hospital site in the United Kingdom. We are a component of the Mahidol-Oxford Research Unit (MORU) Network, with HQ in the Faculty of Tropical Medicine, Mahidol University, Bangkok, and are greatly assisted by the supplies, logistic and accounting staff of MORU. We

have many scientific liaisons with MORU; ~40% of our research is jointly with MORU-Bangkok.

MORU, the Shoklo Malaria Research Unit (SMRU, in Mae Sot, Thailand), the Cambodia-Oxford Medical Research Unit (COMRU), Myanmar Oxford Clinical Research Unit (MOCRU), Kinshasa Mahidol Oxford Research Unit (KIMORU) in the Democratic Republic of the Congo, and LOMWRU are integrated into the Thailand Major Overseas Programme of the Wellcome Trust and Oxford University. We are also linked to the Oxford University Clinical Research Unit (OUCRU), based in Ho Chi Minh City, Vietnam, and have important collaborations with them. We are very grateful for all the help of MORU-Bangkok for vital logistical and auditing support for LOMWRU.

We have been part of the WorldWide Antimalarial Resistance Network (WWARN) for 6 years. WWARN maps evidence on antimalarial resistance and treatment and includes published data from Laos, and at Mahosot we run the WWARN Antimalarial Quality group and mapping system (http://www.wwarn.org/aqsurveyor/). This system is being extended to other infectious diseases under the Infectious Disease Data Observatory (https://www.iddo.org/medicine-quality) umbrella and we are expanding our work to map the quality of a diversity of essential medicines. These data are being graded, mapped and released progressively during 2018 as part of the Wellcome Trust funded MAPQAMP project.

The Microbiology Laboratory and LOMWRU together are staffed by 29 Lao Government staff and 49 project-funded staff; 88% are Lao and 56% are female. In addition, we have goats, resident in the Laboratory garden, which assist with the preparation of blood agar. LOMWRU has received significant recent support, in addition to the core funding from the Wellcome Trust, from the US Naval Medical Research Centre, the Bill & Melinda Gates Foundation, the European Union, Department for International Development-UK (DFID), New Zealand e-Asia, Fondation Total/Institute Pasteur, Global Good, DTRA, Global Antibiotic Resistance Partnership, and the Asian Development Bank. Considerable assistance in kind is given by the Institut de Recherche pour le Développement (IRD)/Aix-Marseille University, France, and the Rickettsial Diseases Research Program, Naval Medical Research Center, USA.



Dr Tehmina Barucha with her poster at ASTMH, Baltimore, November 2017

LOMWRU supports the infectious disease diagnostic service of Mahosot Hospital and assists provincial hospitals in the far northwest (Luang Nam Tha), the northeast (Xieng Khouang), the far south (Salavan) and other hospitals and institutions on request, as well as performing clinical research and building diagnostic and research human capacity. In 2017 the Laboratory processed blood cultures from 2,958 patients, cerebrospinal fluid from 181, urine from 1,794, stool from 532, pus from 1,041, genital swabs from 3,625, other body fluids from 292, cryptococcal antigen tests from 260 and throat swabs from 1,782 patients. Dengue IgM and NS1 ELISAs were performed for 1,931 patients, JEV IgM ELISAs for 699 patients, scrub typhus and murine typhus rapid diagnostic tests (RDTs) for 1,397 patients and dengue RDTs for 1,305 patients. LOMWRU also works with the Centre for Malariology, Parasitology and Entomology (CMPE) on malaria projects in the five southern provinces, with the Food and Drug Department on the quality of medicines, with the Bureau of Food and Drug Inspection & Food and Drug Quality Control Centre on the evaluation of innovative medicine quality screening devices and with the Ministry of Health Department of Communicable Disease Control (DCDC) on antibiotic resistance.

Now that there is more information on public health in Laos we are increasing our public and health worker engagement, from the Lao Medical Journal, the University of Health Sciences e-library, to the Targeted Malaria Elimination engagement and the first Science Café in Laos.

In 2017 we published or have in press 43 publications, including 39 peer-reviewed papers, one letter and three book chapters. Since 2000 LOMWRU staff

STAFF AND HUMAN CAPACITY BUILDING

In Memory of Mr Philippe Brossmann, LOMWRU English teacher, and husband of Anisone Chanthongthip, who tragically died on Thursday 25 May 2017

have published 332 papers and book chapters. Here we describe this work and briefly summarize diverse activities over the past year.

With very great sadness, Mr Philippe Brossmann, LOMWRU English teacher and husband of Anisone Chanthongthip, died on Thursday 25 May 2017. He is greatly missed.

New staff who joined in 2017/2018 include, in alphabetical order:

Dr Laddaphone Bounvilay - Research Physician
Mr Olivier Celhay - Mathematical Modeller
Dr Tomas-Paul Cusack - Research Physician
Ms Souksavanh Duangmala - Follow Up Nurse
Dr Anousin Homsana - Research Physician
Mr Khamxeng Khounpaseuth - Laboratory Technician - EFS2 Study
Ms Palingnaphone Koummalasy- Research Assistant
Dr Rebecca Inglis - Research Physician
Ms Yixiao Lu - Research Assistant
Dr Kerryn Moore - PneuCAPTIVE Coordinator
Mr Theophilus Ndorbor - WHO/TDR Fellow - Medicine Quality
Mr Sonexay Phalivong - Project Coordinator - Malaria-Genetic Reconnaissance Study
Ms Khwanta Phanmany – Laboratory technician – EFS2 study
Dr Vilayouth Phimolsarnnusith - Research Physician
Mr Vanheuang Phommadeechak - Lab Technician BSL3
Mr Soulideth Sengkhamyong - Specimen Storage Technician
Ms Vayouly Vidhamaly - Research Assistant - Medicine Quality
Mr Parnthong Xaithilath - Data Entry Officer
Dr Xaipasong Xaiyaphet - Research Physician
Mr Pao Yang – IT Support
Dr Souphalak Inthaphatha - Research Physician (EFS-Saravane)

Three Lao postgraduate fellows in infectious disease have been conducting their University of Health Sciences research with us and have successfully defended their theses:

Dr Phouvieng Douangdala – 'Neurological Outcomes of *Japanese Encephalitis Virus* (JEV) Infection in Paediatric and Adult Patients at Mahosot Hospital, Vientiane, Lao PDR'. He presented a poster describing these data at the American Society of Tropical Medicine & Hygiene in the USA in November 2017, supported by the Society.

Dr Ko Chang – 'Epidemiology of Extend Spectrum Beta-lactamase in Lao PDR'.

Dr Savandalat Phouangsouvanh – 'The antibiotic susceptibility pattern of *Neisseria gonorrhoeae* in the samples test cultured at Microbiology Laboratory, Mahosot Hospital during 2011-2015'.

Dr Bandith Soumphonphakdy (on respiratory infections) will complete his in 2018.

Dr Nilundone Senvanpan successfully completed her Institut de la Francophonie pour la Médecine Tropicale (IFMT) MSc thesis on a 'Pilot-study of the seroprevalence of antibodies against three pathogens associated with wildlife-borne diseases in vegetable, as well as domestic and wildlife meat vendors in Lao markets'.

Ms Yixiao Lu successfully completed her IFMT MSc thesis on an 'Evaluation of the Performance of Two Commercial ELISA Kits for the Detection of Anti-Dengue IgM for Routine Dengue Diagnosis in Serum Samples and Cerebrospinal Fluid'.

Dr Koukeo Phommasone is analysing and writing up his University of Amsterdam PhD fieldwork, Dr Tiengkham Pongvongsa his Mahidol University PhD fieldwork and Dr Bipin Adhikari his Oxford University DPhil as part of the TME project in Savannakhet Province.

Mr Weerawat Phuklia is conducting his Mahidol University PhD on the antibiotic susceptibility of diverse isolates of *O. tsutsugamushi*.

Dr Ivo Elliott is conducting his fieldwork on scrub typhus for his Oxford DPhil thesis, spending much time trapping rodents and identifying chiggers.

Dr Tin Ohn Myat and Dr Win Thandar Oo, from Medical University-1 in Yangon, visited us for two and one month respectively, to conduct molecular assays on samples collected in Yangon General Hospital, as part of University of Otago collaboration with Professor John Crump. This work will form part of Dr Tin Ohn Myat's PhD thesis.

Ms Jennifer Boss, from the London School of Hygiene and Tropical Medicine, successfully completed her MSc thesis on 'Antimicrobial susceptibility testing of *Leptospira* spp. in the Lao People's Democratic Republic using disk diffusion'.

Ms Sarah Cassidy-Seyoum, also from the London School of Hygiene and Tropical Medicine, successfully completed her MSc thesis on 'Amplification and Sequencing of the Dengue Virus (1-4) Envelope gene from Rapid Diagnostic Tests Performed in Lao PDR: A Molecular Epidemiological Tool'.

Ms Maria Chiara Rizzi visited us for 5 months from the University of Pavia working on the project 'Testing the role of RDTs as a Point of Care tool in the early diagnosis of melioidosis: a pilot comparison with culture in Laos, an endemic region'.

Dr Tehmina Bharucha returned to LOMWRU for six months from University College, London, and conducted virology research on JEV and CNS infections and Dr Damien Ming visited for six months from Imperial College, London, working on *Angiostrongylus* infections and murine typhus.

Dr Rebecca Inglis started work in April 2017 on her Oxford DPhil mixed methods research on intensive care units (ICU) in Laos to inform the design of a Lao-run ICU course.

Ms Audrey Rachlin, who previously completed her LSHTM MSc project with us, is now undertaking a PhD at the Menzies School of Health Research in Darwin, Australia, on 'Environmental sources and distribution of *Burkholderia pseudomallei* infection in northern Australia and Lao People's Democratic Republic'.

Dr Cat Wootton is conducting dermatology projects in collaboration with the University of Health Sciences and LOMWRU.

Mr Rupert Weaver visited us for a month from the University of Melbourne, to work with the PneuCAPTIVE team on hypoxic pneumonia.

Ms Isabelle Pearson visited from Tsinghua University, Beijing, for one month and helped organising our rickettsial literature and with Mandarin translation. Mr Joshua Montgomery from University of Wollongong, Australia, spent an internship with us helping with data entry.

Ms Malee Seephone spent three months in the Unit of Emerging Viruses of Professor Xavier Nicolas de Lamballerie, Faculty of Medicine in Marseille, France, working with Dr Audrey Dubot-Pérès, funded by the Institut de Recherche pour le Développement (IRD).

Farewell Basci to thank Dr Rene Niehus

Dr Audrey Dubot-Pérès, who leads the LOMWRU virology, is based in Marseille but returned for her traditional three months of intensive virology work in LOMWRU in 2017. Ms Bountoy Sibounheuang is now studying for the BSc in Medical Technology at Khon Kaen University. Dr Boris Pastorino visited for 6 weeks for virology support and training in cell culture and virus isolation, funded by IRD.

We are fortunate to have strong links with Public Health England (PHE) who have supported Dr Thomas-Paul Cusack, a UK microbiology/infectious disease registrar to spend a year with us in 2017-2018.

Ms Jana Lai from Australia has been working with us on the PneuCAPTIVE study and left in December 2017 and her successor is Dr Kerryn Moore.

In 2017 we supported 12 Lao staff to attend 6 international meetings and short courses.

Numerous students and doctors in diverse health disciplines studied in the Microbiology Laboratory in 2017. The Laboratory staff assisted with the post-graduate internal medicine and paediatric training programme teaching.

Dr Matthew Robinson and Dr Pruksa Nawtaisong taught on a vector-borne disease course organised by Institut Pasteur du Laos and the Lao Ministry of Defence. Regular classes have been held in English language.

Dr Rene Niehus, Mr Olivier Celhay, Dr Khansoudaphone Phakhounthong and Dr Phetsavanh Chanthavilay ran a Data Science workshop. MORU-Bangkok is also planning a 'mathematical modelling for policymakers' workshop in Vientiane for 2018.

Ms Zoe Duran, Mrs Naomi Waithira and Khun Jaruwan Tubprasert, from MORU-Bangkok, ran a Good Clinical Practice course in December 2017. Ms Sophea Sout from NMRC-A taught a USA Collaborative Institutional Training Initiative (CITI) training course on medical research and ethics and eight LOMWRU staff qualified.

Mr Theophilus Ndorbor, WHO/TDR Fellow, from the Liberian Medicine Regulatory Authority,

The Chigger Football Team

is spending 2018 with us, working on West African MRA engagement and reviewing the global evidence on the quality of cardiovascular medicines.

As part of the LACANET project we were able to purchase a quantitative respiratory protection mask fit tester for long term use by both Mahosot Microbiology Laboratory and National Animal Health Laboratory BSL3 lab staff.

We run a monthly journal club, have regular talks and participate in the Mahosot Hospital scientific monthly talks. We also regularly join MORU colleagues via Webex for scientific seminars. LOMWRU staff teach at the University of Health Sciences (UHS) and Institut de la Francophonie pour la Médecine Tropicale (IFMT), Vientiane, the DTM&H of the London School of Hygiene and Tropical Medicine and the International Health MSc at the University of Oxford.

We have continued to build capacity within the Unit with hands-on training in microbiology, clinical history taking, examination and case presentation, ELISA, molecular diagnostic and BSL3 Laboratory work. In addition we have daily *ad hoc* teaching during board rounds and weekly teaching sessions for the doctors working within the Unit (both at Mahosot and those visiting from the Provinces) covering clinical and laboratory aspects of infectious diseases and microbiology directly relevant to both their clinical and research activities. We have a Lao Clinical Safety Officer, two Lao Deputy Safety Officers, a Lao Head of Field Research, a Lao Deputy Head of Virology, a Lao Administrator, a Lao Deputy WWARN Antimalarial Quality Coordinator, and a Lao Laboratory Manager. A Laboratory Management Adviser is co-ordinating a programme of work towards ISO15189 accreditation for the Microbiology Laboratory, and we are working closely with other laboratories in Laos, working towards such accreditation.

The Laboratory football team, 'The Chiggers', play weekly in Vientiane. Recent notable victories include playing the Australian Embassy team, winning 8:6, and the Banque pour le Commerce Exterieur Lao Public, winning 5:3 – congratulations to The Chiggers!

New Staff 2017

Mr Khamxeng Khounpaseuth
Lab Technician
NRCS-EFS 2 Study

Mr Sonexay Phalivong
Project Coordinator
Malaria-Genetic
Reconnaissance Study

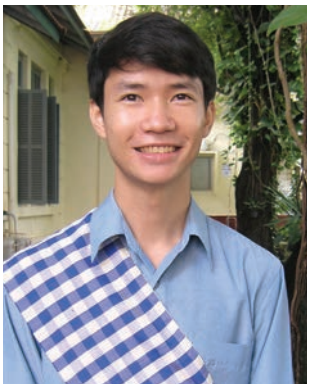
Mr Olivier Celhay
Mathematic Modeller
LOMWRU

Ms Vayouly Vidhamaly
Research Assistant
LOMWRU

Dr Tomas-Paul Cusack
Research Physician
LOMWRU

Mr Soulideth Sengkhamyong
Specimens Storage
LOMWRU

Dr Souphalak Inthaphatha
Research Physician (EFS-Saravane)
LOMWRU



Dr Anousin Homsana
Research Physician
LOMWRU

Dr Vilayouth Phimolsarnnusith
Research Physician
LOMWRU

Dr Xaipasong Xaiyaphet
Research Physician
LOMWRU

Dr Kerryn Moore
Research Physician
PneuCAPTIVE Project
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Ms Palingnaphone Koummalasy
Research Assistant
LOMWRU

Mr Pao Yang
IT Support Manager
LOMWRU

Ms Maria Rizzi
Researcher
LOMWRU

RESEARCH RESULTS AND THEIR PUBLIC HEALTH IMPLICATIONS

FIEBRE Collaboration Meeting London May 2017

1. Infectious Disease Diagnosis, Epidemiology and Treatment

We continue to report every month all clinically significant positive blood, cerebrospinal fluid and genital swab culture results and their antibiotic susceptibility profiles, through the Monthly Microbiology Summary, to the Lao Ministry of Health, National Centre for Epidemiology and Laboratory (NCLE), National Animal Health Laboratory, other hospitals in Vientiane and WHO.

A. Fever in rural Laos. The data published by Mayxay *et al.* (2013) in Lancet Global Health (see 2014 Annual Report) demonstrated the importance of a wide spectrum of neglected infectious diseases, especially dengue, scrub typhus, leptospirosis and the *Japanese encephalitis virus*, as the causes of non-malarial fever in patients in rural Laos.

We expanded this work in 2015, as the Expanded Fever Surveillance (EFS) project with the support of the US Naval Medical Research Centre, to include Xieng Khouang Provincial Hospital (XK) in the Plain of Jars, along with those in Salavan (SV) and Luang Nam Tha (LNT), investigating the aetiology of fever in outpatients. The National Centre for Laboratory & Epidemiology (NCLE) has analyzed nasopharyngeal swabs from these patients, contributing to national influenza surveillance. Outpatients of any age giving informed written consent were recruited to EFS, if they presented with history of fever for ≤8 days and/or admission temperature ≥38°C, during the study blocks. Each week was divided into ten slots in which outpatients were seen and study blocks were chosen using random numbers. This gave a total recruitment time of 51% of the time outpatients were seen.

It commenced on the 1st December 2014 and was completed on 30th November 2015. A total of 2,070 patients were recruited (900 from Luang-Namtha (LNT), 576 from Xieng Khouang (XK) and 594 from Salavan (SV)). 21 patients (1%) were admitted from the outpatient department to the hospitals. The majority of the recruited patients were children less

than 15 years old (60%), with a median (range) age of 9 (2 days to 85 years) years old, and just over half of them (52%) were male.

Influenza PCR could not be completed for all recruited patients from 1st of September 2015 until the end of this study, so a random selection of one day a week was chosen. Of the 2,070 patients, 347 (17%) were given a conservative laboratory diagnosis, 175 (20%) at LNT, 65 (11%) at SV and 107 (19%) at XK. The main diagnoses were influenza (60%), followed by leptospirosis (15%), dengue (10%), scrub typhus and bacteraemia (both 5%), murine typhus (3%), JEV and *Rickettsia* spp. (both 1%).

The main diagnosis at LNT was influenza (72%), leptospirosis was the second most frequently found (11%), followed by dengue (8%), scrub typhus (4%), JEV and *Rickettsia* spp. (both 2%), bacteraemia (1%) and murine typhus (0.5%). The main diagnoses at SV were also influenza (34%), leptospirosis (27%), followed by dengue (12%), bacteraemia (10%), JEV, scrub typhus (8%) murine typhus (7%) and *Rickettsia* spp. (2%). The main diagnoses at XK were influenza (56%) and leptospirosis (13%), followed by dengue (11%), bacteraemia (10%), scrub typhus (5%) and murine typhus (3%), and JEV (2%). The final diagnostic data will soon be ready and the final analysis performed.

We restarted this study as EFS-2, with continued Naval Medical Research Centre-Asia support, at the three provincial hospitals in August 2017 to investigate the aetiology of fever in inpatients. Recruitment is progressing well. We are also looking in the stored blood samples of patients without an aetiological diagnosis for diverse other pathogens such as *Bartonella* spp., *Neorickettsia sennetsu*, *Anaplasma* and *Ehrlichia* species at the three provincial sites and at Mahosot Hospital (see below).

Working with Professor David Mabey and Dr Heidi Hopkins and colleagues at the London School of Hygiene & Tropical Medicine we are planning the multi-country FIEBRE study, funded by the UK Department for International Development. This consensus protocol investigation of the aetiology of fever will be conducted in Myanmar, Malawi, Mozambique, Zimbabwe, Malawi and Laos. In Laos we hope to start this project at Vientiane Provincial Hospital, after Pii Mai Lao.

Dr Pruksa Nawtaisong working in the laboratory

B. Causes of fever at Mahosot Hospital. We are working on amalgamating all the data on common causes of fever (conventional bacteraemia, rickettsia, leptospira, dengue and JEV) over four recent years so that we can estimate the frequency of hospital admission of diverse aetiologies for a large series of patients and describe their comparative clinical features. For the 'conventional' bacteria we are also analyzing how antimicrobial resistance patterns have changed since 2000 and are working with mathematical modelers in MORU-Bangkok to try to understand this better. We work with Stanford University on messenger RNA signatures in infections, especially investigating whether the mRNA signature of scrub typhus is especially characteristic of this disease.

C. Central nervous system (CNS) infections. Central nervous system (CNS) infections are important causes of mortality and morbidity in Southeast Asia. Little is known about their aetiology and impact in Laos. We have completed analyzing the data from the first 1,065 patients to have a lumbar puncture at Mahosot Hospital since 2003. We recruited patients of all ages admitted to Mahosot Hospital, Vientiane, with suspected

CNS infection (2003-2011); 1,065 patients had no contraindications and consented to lumbar puncture. Aetiology was confirmed in 450 (42.3%) patients of whom 93.6% had abnormal CSF. The aetiologies were *Japanese encephalitis virus* in 94 (8.8%) patients, *Cryptococcus* spp. in 70 (6.6%), *O. tsutsugamushi* in 31 (2.9%), *Dengue virus* in 27 (2.5%), *Leptospira* spp. in 25 (2.3%), *Rickettsia* spp. in 24 (2.3%), *Streptococcus pneumoniae* in 22 (2.1%), *Mycobacterium tuberculosis* in 20 (1.9%), *Herpes simplex virus* (HSV) (1.4%), *Human cytomegalovirus* (HCMV) 12 (1.1%), *Human enterovirus* (0.9%), varicella-zoster virus (VZV) (0.6%), *Mumps virus* (0.5%) and *P. falciparum* (0.4%). The mortality was high at 26.3%.

Factors that showed strong association with death were higher CSF lactate (p=0.001) and lower GCS (p<0.001). Patients with viral infection more frequently had neck stiffness than those without (AOR 1.9, 95%CI 1.3-2.8). Patients with bacterial infection had higher cerebrospinal fluid lactate (AOR 1.1, 95%CI 1.1-1.2) and serum CRP (AOR 1.0, 95%CI 1.0-1.0) and were more likely to have a history of diabetes (AOR 3.08, 95%CI 1.27-7.46) than those without bacterial infection. The responsible pathogens spanned encephalitis and meningitis without clearly distinguishable clinical manifestations by aetiology.

No clinical/laboratory variables could reliably guide selection of antibiotics. With the importance of rickettsial pathogens, first line treatment with both ceftriaxone and doxycycline should be considered for suspected CNS infection. Lao data suggest that particular attention must be paid to patients who present with decreased Glasgow Coma Score (GCS) and high CSF lactate, who are more likely to die, and the provision of supportive care for unconscious patients, such as high-dependency units (HDU), along with appropriate urgent antimicrobial therapy, may be key factors in improving outcome. With the increasing global prevalence of diabetes, further investigation of the relationship between hyperglycaemia and bacterial CNS infection is needed. This is a collaborative project with multiple partners, especially with IRD/ Aix-Marseille University, France.

The majority of CSF samples collected gave abnormal results, suggesting that a higher frequency of lumbar puncture is needed to ensure that serious CNS infections are not missed, especially in patients at the extremes of age.

Conventional descriptions of central nervous system (CNS) infections are variably categorised into clinical syndromes for patient investigation, management and research. Aetiologies of the most commonly recognised syndromes, encephalitis and meningitis, tend to be attributed predominantly to viruses and bacteria, respectively. We reviewed aetiological studies of CNS syndromes by reported author specialities (Bharucha *et al.* in press). This identified an association between the author's speciality and the CNS syndrome studied, with a tendency for virologists to study encephalitis, and microbiologists to study meningitis, suggesting that stronger multidisciplinary collaboration in CNS infection research is needed.

We work with the Centre d'Infectiologie Christophe Mérieux du Laos on detection of molecular markers of *M. tuberculosis* drug resistance from patients with TB meningitis. We have been working with Dr Sarosh Irani, Head of the Oxford Autoimmune Neurology Group, who has found evidence of autoimmune central nervous system disease in Lao patients – this will be pursued further in 2018. We have also been working with Professor Nicole Zitzmann and Dr Bevin Gangadharan of the Department of Biochemistry, Oxford, on a search for proteomic signatures in the CSF and sera of patients with Japanese encephalitis infection and clinical encephalitis.

The CNS work was expanded in 2014 as the 'SEAe project' in collaboration with the Institut Pasteur, Paris, funded by the Fondation Total, to investigate the aetiology and impact of encephalitis and meningoencephalitis in Vietnam (at National Institute of Hygiene and Epidemiology & National Children's Hospital, Hanoi), Cambodia (at Kantha Bopha Hospital, Phnom Penh), Laos (at Mahosot Hospital and the Childrens' Hospital) and Myanmar (Yangon Childrens' Hospital) using common study protocols. This allows first line PCR diagnosis of 21 pathogens in the first 24 hours after LP. This project has been completed and the data are being analysed.

D. Aetiology and impact of fever in pregnancy. The large pilot cohort study of the causes and impact of fevers in pregnancy in Pak Gnum District, Vientiane, is completed and analysis is awaiting the final diagnostic data. This study was linked to the National Centre of Laboratory and Epidemiology for surveillance of respiratory infections in pregnant women, supported by US CDC in Laos. One thousand pregnant women

Farewell Basci to thank Maria Chiara Rizzi and Gaye Proctor

were recruited, 92% of all pregnant women known in the district, of whom 110 developed intra-or post-partum fevers. The aetiologies of fever are being examined in relation to outcome measures such as low birth weight and stillbirth. Among the 1,000 women there were 18 miscarriages, 6 perinatal deaths, 3 neonatal deaths, 1 maternal death (ectopic pregnancy) and 11 congenital abnormalities.

Chansamouth *et al.* (2017) discussed the ethical challenges in enrolling pregnant women in research as a part of this large pregnancy cohort study. Level of education, cultural norms about family decision-making, and misconceptions about healthcare during pregnancy were three common issues encountered in enrolling pregnant women. Forty-seven percent of recruited women had completed primary school with no further education, which could affect the decisions women make to participate and remain in the study. Family decision-making is common in Laos; in some cases, we could not recruit pregnant women without agreement from their families. In Laos, many pregnant women and their families had strong beliefs that travelling during late pregnancy or losing a small amount of blood could negatively impact their pregnancies. These misconceptions affected not only the quality of the study but also the women's opportunities to access healtahcare. Good engagement between the research team and study participants, and the provision of more health information to the community, were essential to reducing issues experienced in enrolling pregnant women in this study.

E. Mapping of fevers. We are working with the London School of Hygiene & Tropical Medicine (LSHTM), the Infectious Diseases Data Observatory (IDDO) and the Foundation for Innovative New Diagnostics (FIND) on the mapping of the aetiology of fevers globally, building on our earlier collaboration - Acestor *et al.* (2012; *PLoS One 7,* e44269). These data will be mapped as a part of the Infectious Diseases Data Observatory.

F. How many human pathogens are there in Laos? Temporal trend analysis using discovery-curves has been used to estimate organism diversity – for example, how many tree species are there globally? For her LSHTM MSc thesis, Madeleine Clarkson, with modelling supervision by Dr Ricardo Aguas in MORU-Bangkok/Oxford, applied a similar methodology to country-level data from Laos in order to estimate the total diversity of pathogens available for discovery in Laos and answer the question: 'how many human pathogens are there in Laos'? The Lao dataset was compiled from searches of French and English archival and recent publications, spanning the period 1874 – 2016.

A dataset of 5140 data points was collected through an extensive literature search. The data were graded according to the level of diagnostic evidence used in discovery. Two hundred and thirty-nine species-level data points, with some species repetitions for different grades of evidence, were identified for inclusion in the analysis. The investigation juxtaposed the data with the history of Laos for the 143 year period under investigation prior to modelling to address data gaps and other data novelties. Up to 2016, 159 pathogens have been described in Laos by culture and PCR.

Previous discovery-curve models were improved upon by implementing a time-varying discovery rate in the model to account for observed changes in rate of pathogen discovery. The models estimated between 170 and 196 total species of human pathogens are available for discovery in Laos. This implied that between 10 and 11 new additional species remained available for discovery at the end of 2016. The model

also captured a 36-fold increase in the rate of pathogen discovery during the last ten years due to laboratory and technical advances. The changes in rates of pathogen description can be related to the different phases of Lao history over the 142 years of investigation.

G. Novel incubators. We worked with Global Good on evaluating new incubators for use in the tropics. These were trialled at Mahosot and in Luang Nam Tha and Salavan Provincial Hospitals. The monitoring data are being used by Global Good to optimise the incubators and a paper describing this work has been submitted.

H. Novel diagnostics. We are evaluating new simplified systems for molecular diagnostics, including the miniPCR system and novel recombinase polymerase amplification (RPA) assays using lateral flow tests for *O. tsutsugamushi* molecular detection. We are also evaluating the Biofire Travellers molecular detection system.

I. Appropriate diagnostics. We participated in a project reviewing the infrastructural, technical and behavioural challenges that low resource settings (LRS) face when implementing clinical bacteriology – that is a prerequisite for effective AMR control (Ombelet *et al.* in press). The majority of microbiological techniques and equipment have not been developed for the specific needs of LRS and that pending the arrival of a new generation of LRS-friendly diagnostics, improving, adapting and implementing conventional, culture-based techniques are required. LRS priorities should include harmonized, quality-assured and "tropicalized" equipment, consumables and techniques as well as rationalized bacterial identification and AMR testing. Furthermore, diagnostics should be integrated into clinical care and patient management. Clinically relevant specimens must be appropriately selected and prioritized. Open-access training materials and information management tools should be developed. The team advocated on-site validation and field-adoption of diagnostics in LRS, with considerable shortening of the time between development and implementation of diagnostics. Implementing clinical bacteriology in LRS will improve patient management, provides valuable surveillance for local antibiotic treatment guidelines and national policies, and augments AMR containment and hospital infection prevention and control.

J. *Angiostrongylus cantonensis* infection. *A. cantonensis* (the rat lungworm) has long been suspected as a cause of eosinophilic meningitis in Laos and with the description of a new qPCR assay for detecting DNA of this worm in CSF we have demonstrated, among 36 patients with eosinophilic meningitis, that 4 (11.1%) were *A. cantonensis* PCR positive (Ming *et al.* 2017). This finding has One Health implications for public engagement in Laos for safe eating habits (below).

We are part of a new international collaboration with the Rat Lungworm Consortium. The rat lungworm infects humans via consumption of raw or undercooked snails (the intermediate hosts), crabs, frogs and prawns (paratenic hosts), all of which are common food items in Laos. Rats, the main host of the worm, are also commonly sold at markets. In humans the worms may migrate into the brain, where the resulting death of the worms and host immune response can cause mild to fatal neurological damage. LOMWRU is one of seven key partners in this multidisciplinary consortium, funded by the Worldwide Universities Network.

K. Febrile Illness in Adolescents and Adults. Working with colleagues in MORU and University of Otago we reviewed evidence on management of febrile illness in adolescents and adults (Crump *et al.* 2017).

L. Diabetes mellitus. Because of the importance of diabetes as a risk for melioidosis and tuberculosis, and the apparent high prevalence in Vientiane, we have started a pilot study to examine the clinical and biochemical phenotype of diabetes in Vientiane in collaboration with Setthathirat Hospital.

2. Clinical Bacteriology, Melioidosis & AMR

A. Extended spectrum beta-lactamase (ESBL) carriage in a remote Lao village. We estimated the prevalence of colonisation with ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* in a remote village, Yod Teui, in Xieng Khouang Province. Rectal swabs were taken from 268 human inhabitants and 252 domestic animals. Overall 14 humans and 21 animals (including chickens, dogs and pigs) were found to be colonised with ESBL-positive organisms, despite the remoteness of the village and the fact that no commercial animal feedstuffs were being used. However, a surprising proportion of the human population (13.4%) self-reported taking antibiotics in the preceding two weeks.

Further data analysis is underway and whole genome sequencing of the isolates is being undertaken in order to investigate the epidemiology of antimicrobial resistance within this relatively isolated community.

B. Extended spectrum beta-lactamase (ESBL) acquisition amongst visitors to Laos. The acquisition of ESBL-producing *E. coli* and *K. pneumoniae* was studied amongst 21 European doctors participating in a tropical medicine course in Vientiane during September and October 2015, by collecting daily rectal swabs. Ten of the participants were already excreting organisms that grew on the selective screening medium by the time they submitted their first sample, and all of the participants had had one or more probable ESBL positive cultures by the end of the course of three weeks. Further characterisation of these isolates and data analysis are underway. These data suggest that ESBL bacteria are abundant in people and the environment in Vientiane and visitors rapidly become colonised, risking their health and the dissemination of these bacteria elsewhere.

C. Carbapenem-resistant Gram negative bacilli in Laos. We have found the first isolates of carbapenem-resistant *E. coli* and *Acinetobacter* species in Laos. The *E. coli* included isolates from pus, the urinary tract and one case of bacteraemia, whilst the Acinetobacters were mainly isolated from respiratory samples from the Intensive Care Unit of Mahosot Hospital. With the recent beginning of use of carbapenems in Laos this is extremely worrying and calls for increasing oversight of their use. Further characterization of these isolates and identification of the resistance mechanisms are underway.

D. *Burkholderia pseudomallei* and the environment. Dr Rosalie Zimmermann was awarded the highest grade possible by the University of Basel, Switzerland, for her Master's thesis on the presence of *B. pseudomallei* in tributaries of the Mekong River which was reported in last year's annual report and has been submitted for publication. Further work to study the microbial diversity in these samples and to evaluate a variety of different molecular methods for direct quantitative detection of *B. pseudomallei* in these samples is underway.

The manuscript from Dr Loungnilanh Manivanh's IFMT Master's project was published in Nature Scientific Reports (Manivanh *et al.* 2017). This study raised the possibility that *B. pseudomallei* might occupy specific micro-niches within soil and that previous studies may have missed associations with specific physico-chemical conditions by pooling soil samples prior to analysis. Further work to investigate this possibility is in progress. During this study it was noted that samples were frequently positive by direct culture on agar plates but negative following enrichment broth culture, calling into question the published international consensus method for culturing soil for *B. pseudomallei* which is based on broth enrichment. A formal evaluation of the consensus method compared with the more labour-intensive surface plate cultures and molecular methods found that, of 100 samples collected from a rice field in Vientiane Province that was known to be heavily colonized with *B. pseudomallei*, only 10 were positive by the consensus method compared with 42 by surface plate culture and 84 by PCR following enrichment. These findings confirm that the consensus method may not work equally well in all environments and may give rise to false-negative results. A paper describing these results is in preparation.

During 2017 we obtained funding from DTRA, in collaboration with Dr Todd French of the University of California, to conduct a 3-year study entitled 'Eco-environmental signatures of danger to identify melioidosis-endemic hotzones'. The objective of this project is to Identify and characterize environmental factors and relationships between *B. pseudomallei* and co-endemic species, and explore how these affect the survival and virulence of *B. pseudomallei*. We also aim to determine their subsequent effects on disease incidence in humans and mammals, to establish ecological signatures of virulence potential and endemicity to improve prediction and surveillance, and evaluate the utility of co-endemic predator and host species for diagnostic identification and biocontrol efforts. Dr Wayne Wong visited in late 2017 to undertake an initial round of sampling for this project and he confirmed that the rice field in Vientiane Province which we have studied previously remains heavily colonized by *B. pseudomallei*, but he was unable to detect the organism in samples from a rice field in Luang Prabang Province.

Audrey Rachlin, who previously undertook a LSHTM Master's project looking at recurrent melioidosis in Laos reported in last year's annual report, is now studying for a PhD at the Menzies School of Health

Research in Australia. She has been finding that *B. pseudomallei* is extensively present throughout urban and suburban Darwin in the Northern Territory of Australia, and during 2017 she visited LOMWRU in order to plan similar studies in Vientiane, which she will undertake during 2018.

We are working with the Myanmar Oxford Clinical Research Unit and the Department of Medical Research in Yangon in studies of *B. pseudomallei* in the environment in Myanmar. These have already yielded many positives, suggesting that melioidosis is probably also being substantially underdiagnosed in Myanmar, although enhanced clinical surveillance in and around Yangon has so far only yielded a handful of cases.

During our environmental studies we have isolated strains of other *Burkholderia* species (*B. thailandensis and B. cepacia*) that cross-react with a monoclonal antibody-based latex agglutination reagent that is used for screening for *B. pseudomallei*. The first such strain of *B. thailandensis* was originally detected in Cambodia, but it has also been found in Laos and it has now been found to be widespread in Thailand as well (Hantrakun *et al.* 2018). The genetics and biochemical basis for these cross-reactions is being studied in collaboration with colleagues at Mahidol University and the Universities of South Alabama and Nevada.

One of the strengths of LOMWRU's work on the ecology of *B. pseudomallei* over the past few years has been the establishment of a collaboration with soil scientists and hydrologists from the Institut de Recherche pour le Développement and the International Water Management Institute, as to date the majority of the work in this area has been conducted by clinical microbiologists. We are planning a multi-national, multi-disciplinary project to analyze the effect of landscape features (soil, land cover, rivers, sediments, etc.) on the presence and transport of *B. pseudomallei* across the Mekong Basin in order to predict contamination hazards under different scenarios of climate and land-use changes and in relation to indicators of susceptibility, in order to reduce risk to populations.

On a global scale Chewapreecha *et al.* (2017) used whole genome sequences of 469 *B. pseudomallei* isolates from 30 countries, including Laos, collected over 79 years to explore its geographic transmission. These data point to Australia as an early reservoir, with transmission to Southeast Asia followed by onward transmission to South Asia and East Asia. Repeated reintroductions were observed within the Malay Peninsula and between countries bordered by the Mekong River. These data support an African origin of the Central and South American isolates with introduction of *B. pseudomallei* into the Americas between 1650 and 1850. They also identified geographically distinct genes/variants in Australasian or Southeast Asian isolates alone, with virulence-associated genes being among those over-represented. This provides a potential explanation for clinical manifestations of melioidosis that are geographically restricted.

E. *Burkholderia pseudomallei* and clinical bacteriology. Since melioidosis was first diagnosed in Laos in 1999, 1,234 culture-positive cases of melioidosis (including 157 in 2016 and 144 in 2017) have been diagnosed by the Mahosot Microbiology Laboratory with support from LOMWRU. Cases have been seen from every province except Luang Namtha, although inevitably the majority have come from Vientiane Capital and Vientiane Province. Once the analysis of this dataset is complete we plan to work with the National Centre for Laboratory and Epidemiology (NCLE) to arrange a Lao national workshop on melioidosis, analogous to the one we helped to organize in Cambodia in 2017, in order to raise awareness of the disease and its management amongst Lao doctors and lab staff. A review of melioidosis in Laos has also been prepared for inclusion in a special issue of the journal 'Tropical Medicine and Infectious Disease' devoted to the global burden and challenges of melioidosis, which is being co-edited by David Dance and Direk Limmathurotsakul from MORU.

One of the reasons for the under-diagnosis of melioidosis in some countries is the difference between local practices of laboratory utilization. This was highlighted in a study comparing blood culture rates in Thailand and Indonesia, which demonstrated far higher rates of laboratory utilization in Thailand in relation to the relative socio-economic status of the two countries (Teerawattanasook *et al.* 2017). We have also assisted in a review on melioidosis and contributed to a workshop on melioidosis in Indonesia, which have revealed growing evidence that melioidosis is under-diagnosed throughout the country.

Culture remains the mainstay of melioidosis diagnostics, but is slow, requires experienced staff, and is associated with potential bio-hazards. We have continued to evaluate a new rapid diagnostic test (RDT) for *B. pseudomallei* antigen detection in clinical samples, the Active Melioidosis Detect lateral flow immunoassay (AMD, InBios International, USA). During the first 2 years of evaluation, AMD was 99% sensitive and 100% specific on turbid blood culture bottles, similar to latex agglutination and immunofluorescence. AMD specificity was 100% on pus (122/122; 97.0-100%), sputum (20/20; 83.2-100%), and sterile fluid (44/44; 92 – 100%), but sensitivity on these samples was moderate: pus 47.1% (8/17; 23.0 – 72.2%), sputum 33.3% (1/3; 0.84 – 90.6%), and sterile fluid 0% (0/2; 0 – 84.2%). Urine AMD had an overall positive predictive value of 94% (32/34; 79.7 – 98.5%) for diagnosing melioidosis. AMD sensitivity on stored sera was 13.9% (5/36; 95% CI 4.7% to 29.5%) when compared to blood culture samples taken on the same day. The AMD thus appears to be a promising tool for diagnosis of melioidosis, particularly by urinary antigen detection, although further work is required to study larger numbers of patients and improve sensitivity on non-blood culture samples.

During 2017, a further evaluation of the AMD was conducted by a visiting medical student from the University of Pavia in Italy, Maria Chiara Rizzi, particularly focusing on the extent to which the new rapid test might speed up the diagnosis of melioidosis. She enrolled 112 patients, of whom 26 were confirmed as having culture-positive melioidosis. The AMD was applied to 106 whole blood, plasma and buffy coat samples, 96 urines, 28 sputum and 20 pus samples. The AMD had an overall sensitivity of 69.2%, a specificity of 87.2%, and positive and negative predictive values of 62% and 90.3% respectively. The issues with specificity were confined to very faint bands seen in some urine samples which were likely to have been false positives. The time to diagnosis was reduced by a mean of 18 hours. These findings confirm that a reliable RDT could improve the management of melioidosis patients. However, the AMD was again found to have disappointing sensitivity and problems of specificity when testing urine. Further work is underway with Dr David Aucoin from the University of Nevada to quantify the amount of extracellular polysaccharide, the antigen detected by the AMD test, in the urine of patients with melioidosis.

In addition to the above, we continue to collaborate with Dr Ivo Steinmetz, who has moved to the University of Graz in Austria, in various melioidosis-related projects including evaluation of his highly sensitive PCR method for the detection of *B. pseudomallei* DNA in EDTA blood. We have also continued to work with Professor K Thong Wong, University of Malaya, on the intracellular localisation of *B. pseudomallei* in human cells. We also collaborated with colleagues at Mahidol University and MORU in a study of the identification of *Burkholderia* species by MALDI-TOF, which confirmed that this method works well for identifying *B. pseudomallei* as long as the correct database is used (Suttisunhakul *et al.* 2017). This will be helpful with difficult strains using the MALDI-TOF at LOMWRU. David Dance also collaborated with colleagues from several countries in a recent comprehensive review of melioidosis (Wiersingha *et al.* 2018).

F. Respiratory infections. We are continuing a prospective description of the clinical features and aetiologies of respiratory illness in children (ARIVI). This has given the first evidence that *Mycoplasma pneumoniae* does occur in Laos. Within this study, and working with the Murdoch Children's Research Institute, Melbourne, we are also estimating the hospital incidence of *S. pneumoniae* invasive disease, pneumococcal carriage and its serotypes to examine how their frequencies change with the introduction of 13 valent *S. pneumoniae* vaccination in Laos – the PneuCAPTIVE study is funded by the Bill & Melinda Gates Foundation. We also work with the Centre d'Infectiologie Christophe Mérieux on the LaCoRIS study, funded by the US Naval Medical Research Centre-Asia, which is a large cohort study examining the aetiology of respiratory illness in the community in Vientiane that has been extended until December 2018.

G. *Clostridium difficile*. There are few data on the epidemiology of *Clostridium difficile* in Asia. We therefore looked for it in the stools of patients at Mahosot Hospital and *C. difficile* was isolated from five of 70 patients; five different ribotypes were identified (014, 017, 020, QX 107 and QX 574) (Cheong *et al.* 2017). The occurrence of this organism is not unexpected with the high cephalosporin use in Vientiane hospitals and argues for enhanced antibiotic stewardship. Otherwise there is a risk of large outbreaks of hospital-associated diarrhoea, including some potentially fatal cases of pseudomembranous colitis.

First Lao Global Antibiotic Resistance Partnership Meeting, Vientiane, May 2017

H. Gonorrhoea. Dr Savandalath Phouangsouvanh, a Lao internal medicine resident, conducted her thesis research to describe the antibiotic susceptibility patterns of *N. gonorrhoeae* in samples cultured at the Microbiology Laboratory, Mahosot Hospital during 2011-2015 (Phouangsouvanh *et al.* 2017). A total of 12,281 genital samples were received during this period and 165 (1.3%) grew *N. gonorrhoeae*. Of 158 isolates with antibiotic susceptibility data, all were susceptible to ceftriaxone and spectinomycin but 84.8% were resistant to ciprofloxacin, 89.9% to penicillin and 99.3% to tetracycline. These data suggest that ceftriaxone and spectinomycin are likely to be efficacious against *N. gonorrhoeae* in Laos. This fortunately means that the latest Lao national guidelines for treating gonorrhoea should be effective. Contact tracing and treatment of partners will be a key intervention to reduce the burden of STIs.

I. *Streptococcus suis*. We are working with OUCRU-Ho Chi Minh City on analysing a case series of Lao *S. suis* isolates, including their genomics and antimicrobial susceptibility, and how differences in pig farming between Vietnam (where *S. suis* is a more frequent cause of meningitis) and Laos may influence this.

J. Azithromycin resistance in *Shigella* spp. Darton *et al.* (2018) assessed the frequency and mechanisms of decreased susceptibility to azithromycin in clinical *Shigella* spp. isolates from Vietnam and Laos and used these data to suggest appropriate susceptibility breakpoints. Of 475 available *Shigella* spp. isolated in Vietnam and Laos between 1994 and 2012, 6/181 *S. flexneri* (3.3%, MIC≥16g/L) and 16/294 *S. sonnei* (5.4%, MIC≥32g/L) were phenotypically resistant to azithromycin. None of these were from in Laos, although 14 of 45 Lao isolates showed resistance to quinolone antibiotics.

K. Non-typhoidal *Salmonella* serovars. Phuong *et al.* (2017) examined the causative serovars of non-typhoidal *Salmonella* invasive (iNTS) and non-invasive disease in Laos. They performed MLST and antimicrobial susceptibility profiling of 168 NTS (63 blood and 105 faecal) organisms isolated in Laos between 2000 and 2012. Six different serovars were

isolated from blood. *S.* Enteritidis, *S.* Typhimurium and *S.* Choleraesuis accounted for >90% of the iNTS cases. In contrast, the isolates from diarrhoeal faeces comprised 18 different serovars, the mostly commonly identified being *S.* Typhimurium, *S.* Weltevreden, and *S.* Stanley. *S.* Enteritidis and *S.* Choleraesuis were significantly more associated with systemic disease than diarrhoeal disease. Organisms isolated from faecal samples were significantly less likely to be susceptible to ampicillin and trimethoprim-sulphamethoxazole than those isolated from blood. The majority of bloodstream isolates were non-susceptible to ciprofloxacin; this proportion was significantly greater than in the organisms isolated from faeces. There is a small but not-insignificant burden of iNTS disease in Laos; further clinical and epidemiological investigations are required to assess mortality and the role of co-morbidities such as HIV.

L. *Staphylococcus aureus.* Yeap et al. (2017) describe the molecular epidemiology of *Staphylococcus aureus* from skin and soft tissue infections (SSTI) in Laos, from a random sample of 96 *S. aureus* SSTI isolates received by the Microbiology Laboratory, Mahosot Hospital, between July 2012 and June 2014. Forty-three *spa* types, representing 17 lineages, were identified. Fifty-eight percent of all isolates encoded Panton-Valentine leukocidin (PVL). The dominant lineage was CC121 (41%); all but one isolate encoded PVL and 49% were from children under five years old.

Staphyococcus argenteus was identified for the first time in Laos, from six (6%) patients; mostly adults >50 years and with diabetes. Six isolates (6%) belonged to rare lineage ST2885; two possibly indicate cross-infection in a neonatal unit. *S. aureus* antibiotic resistance was uncommon except for penicillin (97%) and tetracycline (50%). Seven (7%) isolates were methicillin-resistant *S. aureus* (MRSA). Globally widespread CC5 and CC30 were absent. There are parallels in *S. aureus* molecular epidemiology between Laos and neighbouring countries and these data highlight the prominence of PVL and suggest infiltration of MRSA clones of epidemic potential from surrounding countries.

M. Antibiotic resistance & GARP. With increasing concern globally and in Laos about the public health consequences of antibiotic resistance, we have joined with the Ministry of Health and key stakeholders

The Antibiotic Use Point Prevalence Survey (PPS) team setting off for the first PPS in Laos (Dr Sayaphet Rattanavong, Dr Manophab Luangraj, Dr Tookta Bounkhoun, Dr Onanong Sengvilaipraserth, Dr Danoy Chommanam, Dr Anousone Duangnouvong & Dr Vilada Chansamouth)

E-Asia meeting, August 2017, at University of Medicine ¬1 with Dr Khine Mar Oo, Dr Win Thandar Oo, Dr Than Than Su, Prof Paul Newton, Assoc. Prof Mayfong Mayxay, Prof Wah Win Htike, Prof John Crump, Dr James Ussher, Prof David Murdoch, Prof Hla Hla Win and Assoc. Prof Min Zaw Oo

to form an AMR Technical Working Group that will work synergistically with the WHO/FAO/OIE AMR Committee to accumulate and analyse the current scientific evidence for AMR in Laos. As well as describing the antibiotic susceptibility patterns of common Lao bacteria and antibiotic availability and use, these will be compared with their frequency with adjacent counties. This work is with the Global Antibiotic Resistance Partnership (GARP; www.cddep.org/garp/home) and with OUCRU-Hanoi.

The MORU and OUCRU Networks published a review (Zellweger *et al.* 2017) on Southeast Asia as a global hotspot for the emergence and spread of AMR. The review describes the current AMR situation in Southeast Asia, explored the mechanisms that make Southeast Asia a focal region for the emergence of AMR, and proposed ways in which Southeast Asia could contribute to a global solution.

N. Health seeking behaviour, PPS and antibiotic use. We have conducted the first round of the Global Point Prevalence Survey of Antimicrobial Consumption and Resistance (PPS) (www. http://www.global-pps.com/) at four hospitals in Laos and plan to repeat this three times a year to provide the first estimate of hospital inpatient antibiotic use for the country, monitor changes and use the data to inform optimal prescribing policy.

There are few data describing where and why people seek health care at different levels of health care and at different hospitals in Asian cities. As a part of the University of Otago New Zealand funded e-Asia project, we are working with colleagues in Myanmar and New Zealand to understand this better for Yangon and Vientiane, comparing health-seeking behaviour between the two capitals.

Marco Haenssgen from Oxford is leading a study to improve our understanding of patients' antibiotic-related health behaviour, in Laos and Thailand, to inspire more targeted and unconventional interventions. The project tackles three research questions - What are the manifestations and determinants of problematic antibiotic use in patients' healthcare-seeking pathways? Will people's exposure to a behavioural health systems intervention diffuse or dissipate within

a network of competing healthcare practices? Which proxy indicators facilitate the detection of problematic antibiotic behaviours across and within communities?

O. Antimicrobial Resistance networks. Ashley *et al.* (in press) searched for supranational networks performing AMR surveillance in LMICs and assessed their organisation, methodology, impacts and challenges. Since 2000, 72 supranational networks for AMR surveillance in bacteria, fungi, HIV, TB and malaria involving LMICs were found, with 34 still active. Networks were categorised as WHO/governmental (n=26), academic (n=24), or pharma initiated (n=22). Funding sources varied, with 30 networks receiving public or WHO funding, 25 corporate, 13 trust or foundation, and four funded from more than one source. The biggest challenges faced by these networks has been achieving high coverage across LMICs and complying with the recommended frequency of reporting. Antibiotic resistance surveillance requires a level of laboratory infrastructure and training which is not widely available in LMICs. The nascent Global Antimicrobial Resistance Surveillance System (GLASS) aims to build up passive surveillance in all member states. Past experience suggests complementary active approaches may be needed in many LMICs if representative, clinically relevant, meaningful data are to be obtained.

P. *Streptococcus agalactiae* (Group B Streptococcus - GBS). Following a unique fish-borne outbreak of GBS serotype III, ST283, in Singapore in 2015, we have collaborated with Dr Tim Barkham at Tan Tock Seng Hospital in investigating the regional epidemiology of this organism. Of 38 unique cases of invasive GBS infection diagnosed by LOMWRU since 2000, 29 (76%) were serotype III and ST283 accounted for 28. Invasive GBS ST283 has thus been present in Laos since 2000 and possibly earlier, and appears also to be present in both fish and human infections in neighbouring countries, raising interesting questions about its epidemiology and the role of fish as a source of infection. These results have been presented at international meetings and papers describing the regional situation are in preparation.

3. Leptospirosis

A. Leptospirosis rapid diagnostic tests. Simple rapid diagnostic tests (RDTs) are needed to enable health care workers, particularly in low resource settings, to diagnose leptospirosis early and give timely targeted treatment. We compared four commercially available RDTs to detect human IgM against *Leptospira* spp. in a head-to-head prospective evaluation in Mahosot Hospital. Patients with an acute febrile illness consistent with leptospirosis (n=695) were included in the study during the 2014 rainy season (Dittrich *et al.* 2017). Samples were tested with 4 RDTs: ('Test-it' (Life Assay, South Africa), 'Leptorapide' (Linnodee, Northern Ireland); 'Dual Path Platform' (DPP) (Chembio, USA) and 'SD-IgM' (Standard Diagnostics, South Korea). Diagnostic performance characteristics were calculated and compared to a composite reference standard combining PCR (*rrs*), microscopic agglutination tests (MAT) and culture.

Of all patients investigated, 39/695 (5.6%) were positive by culture, PCR or MAT. The sensitivity and specificity of the RDTs ranged greatly from 17.9-63.6% and 62.1-96.8%, respectively. None of the investigated RDTs reached a sensitivity or specificity of >90% for detecting *Leptospira* infections on admission. This highlights the challenges associated with *Leptospira* diagnostics, particularly in populations with multiple exposures and emphasize the need for extensive prospective evaluations in multiple endemic settings to establish the value of rapid tools for diagnosing fever aetiology. The results are disappointing for Laos in that no leptospiral antibody-detecting RDT was found that could fill the current gap in diagnosing leptospirosis in the country.

B. Comparison of PCR assays for detecting *Leptospira* spp. Woods *et al.* (2017) compared two molecular assays (rrs quantitative PCR (qPCR) versus a combined 16SrRNA and LipL32 qPCR) on different sample types for diagnosing leptospirosis in febrile patients presenting to Mahosot Hospital. *Leptospira* spp. culture and microscopic agglutination tests (MAT) were performed as reference standards. Bayesian latent class modelling was performed to estimate sensitivity and specificity of each diagnostic test. 787 patients were included in the analysis: 0.5% were *Leptospira* culture positive, 3.8% were MAT positive, 9.7% were rrs qPCR positive and 2.5% were 16SrRNA/LipL32 qPCR positive for pathogenic *Leptospira* spp. in at least one sample.

Estimated sensitivity and specificity of 16SrRNA/LipL32 qPCR on serum, buffy coat and urine samples were comparable with those of rrs qPCR, except that

the specificity of 16SrRNA/LipL32 qPCR on urine samples was significantly higher (99.6% vs. 92.5%, p <0.001). Mean positive Cq values showed that buffy coat samples were more frequently inhibitory to qPCR than either serum or urine (p <0.001). Importantly for Laos, serum and urine are better samples for qPCR than buffy coat, and the 16SrRNA/LipL32 qPCR performs better than rrs qPCR on urine. These data suggest that the 16SrRNA/LipL32 qPCR on urine and serum is the current best diagnostic test for leptospirosis in Laos.

C. Genomics of *Leptospira* spp. We are working with Institut Pasteur-Paris to conduct whole genome sequencing (WGS) on the leptospires cultured from patients in the Microbiology Laboratory with comparison with data from other Asian countries and examining the relationship between genomes and antibiotic susceptibility.

D. Susceptibility testing of *Leptospira* spp. Jennifer Boss from the LSHTM conducted antibiotic susceptibility testing of *Leptospira* spp. isolates for her MSc thesis that is being written up as a paper. No evidence of emerging antibiotic resistance was found. These isolates will be sent for WGS at Institut Pasteur in Paris to investigate the relationship between susceptibility and genomes.

4. Rickettsiology and related pathogens

A. Rapid diagnostic tests for scrub typhus. We are conducting a prospective study in 2016/2018 of the diagnostic accuracy of 5 different scrub typhus RDTs to determine which one(s) are the optimal for the diagnosis of this important disease in rural Asia. This will finish in 2018.

B. Scrub typhus genotypes. Collaboration with the Rickettsial Diseases Research Program, Naval Medical Research Center, USA, is progressing with the whole genome sequencing (WGS) of multiple Lao *Orientia tsutsugamushi* genotypes to examine whether different genotypes are associated with disease severity. Twenty isolates have had successful WGS performed and more genotypes will be sequenced by the Oxford Centre for Human Genetics (OCHG). These data will help us understand the genetic diversity of *O. tsutsugamushi* in Laos and if severe scrub typhus and antibiotic susceptibility are associated with particular *O. tsutsugamushi* genotypes.

Farewell Basci to thank Jana Lai

C. Revisiting the natural history of scrub typhus. Dr Ivo Elliott is working on his Wellcome Trust Fellowship research, revisiting the natural history of scrub typhus in the 1930s/1950s using modern techniques such as whole genome sequencing and geographical information systems. There are many uncertainties about the ecology of scrub typhus and this work will increase our understanding and inform interventions to reduce transmission. This is in collaboration with many partners including the Oxford Centre for Human Genetics (OCHG) and the Chiang Rai MORU Unit.

D. Ticks and potential human pathogens. We continued working with the Institut Pasteur du Laos and the US Naval Medical Research Center-Asia, on looking for potential human pathogens, *Rickettsia, Bartonella, Orientia, Anaplasma* and *Ehrlichia* species, in further large collections of ticks from Khammouane Province. A number of samples identified the presence of *Rickettsia* spp. DNA, including *Rickettsia japonica*. In addition, evidence for *Ehrlichia* spp., *Anaplasma* spp. (including *Anaplasma bovis*) and *Leptospira* spp. were identified. This expands our knowledge of tick-borne bacterial pathogens in Laos from previous collections (Taylor *et al.* 2016) and has opened further interesting avenues for investigation, especially regarding the

potential carriage of *Leptospira* spp. in ticks which has only been recently suggested in Europe. We are also collaborating with researchers in Italy to study tick carriage of *Midichloria mitochondii*, an intracellular pathogen of ticks. Our zoonotic vector work continues with the Institut Pasteur du Laos and the US Naval Medical Research Center-Asia with two new projects recently started: further tick and arthropod collections from a village in Khammouane Province, and the study of arthropod vectors from bats, collected from caves, also in Khammouane Province.

E. Mapping and burden of scrub typhus. Bonell *et al.* (2017) reviewed the evidence since the year 2000 to estimate the burden of scrub typhus. Sero-epidemiological data also suggest that *O. tsutsugamushi* infection is common across Asia, with seroprevalence ranging from 9.3%-27.9%. A substantial apparent rise in minimum disease incidence was reported through passive national surveillance systems in South Korea, Japan, China, and Thailand. Mortality reports vary widely around a median mortality of 6.0% for untreated and 1.4% for treated scrub typhus. Limited evidence suggests high mortality in complicated scrub typhus with CNS involvement (13.6% mortality), multi-organ dysfunction (24.1%) and high pregnancy miscarriage rates with poor neonatal outcomes. A wider distribution of scrub typhus beyond Asia is likely, based on reports from South America and Africa.

We are working with VectorMap (http://www.vectormap.org/), the Spatial Ecology and Epidemiology Group of Oxford University, IDDO, University of Liverpool and many partners on the global mapping of chigger vectors/reservoirs and infected rodents and humans. We hope that this result in niche mapping, leading to a greater understanding of the relationships between humans rodents and chiggers in the ecology of scrub typhus and where we should be looking for it.

F. *Bartonella*. With support from the US Navy we have been examining the seroprevalence of *Bartonalla* spp. antibodies in Laos and plan to start molecular diagnosis work in early 2018. We have described *Bartonella* spp. DNA in Lao rural rodent liver & spleens (Angelakis *et al.* 2009) and human *Bartonella henselae* endocarditis (Rattanavong *et al.* 2014). These findings have prompted us to look in more detail at which *Bartonella* species may be human pathogens in Laos and looking for One Health risks.

G. Antibiotic susceptibility of rickettsial species. This project examining the antibiotic susceptibility of diverse isolates of *O. tsutsugamushi,* forming Weerawat Phuklia's PhD, is progressing well and we expect to have more information later in 2018. We plan to expand this work to *R. typhi* and the Spotted Fever group of *Rickettsia* spp.

H. Trials of the antibiotic therapy of uncomplicated murine typhus and scrub typhus. Murine typhus, or infection with *Rickettsia typhi*, is a global but neglected disease without randomised clinical trials to guide antibiotic therapy. Doxycycline is commonly used but without objective evidence for optimum treatment duration. Azithromycin is a potential alternative. We conducted a prospective, open, randomised trial in non-pregnant, consenting inpatient adults with rapid diagnostic test evidence for uncomplicated murine typhus at two hospitals in Vientiane, Laos. Patients were randomised to seven (D7) or three days' (D3) oral doxycycline or three days' oral azithromycin (A3). Primary outcome measures were fever clearance time (FCT) and frequencies of treatment failure and relapse.

Between 2004 and 2009, 216 patients (72 per arm) were enrolled; 158 (73.2%) patients had serology/PCR-confirmed murine typhus; 24.1% were *R. typhi* PCR-positive. All patients survived to discharge. One patient in each treatment group withdrew. Treatment failure risk was greater following regimen A3 (22.5%) compared to D3 (4.2%) or D7 (1.4%) ($p<0.0001$). The area under the time-fever curve and FCT, for *R. typhi* PCR-positive patients, was significantly higher in patients following A3 than D3 (1.8 fold and 1.9 fold, respectively) and D7 (1.5 fold and 1.6 fold, respectively) ($p=0.005$ & $p=0.021$). No patients returned with PCR-confirmed *R. typhi* relapse.

These data have been submitted for publication and suggest that for Lao adults, azithromycin is inferior to doxycycline for the oral therapy of uncomplicated murine typhus. Three and seven days of doxycycline have similar efficacy. Azithromycin use in murine typhus should be reconsidered. Investigation of genomic and phenotypic markers of *R. typhi* azithromycin resistance is needed.

The parallel scrub typhus clinical trial, with the same treatment groups, is being analysed

5. Virology

The virology work of LOMWRU is strongly supported by IRD/ Aix-Marseille University, France. Virological aspects of CNS infections are discussed above. All dengue and JEV surveillance data are reported to the Lao Ministry of Health, National Centre for Epidemiology and Laboratory (NCLE) and WHO, and we work closely with NCLE, Institut Pasteur du Laos and WHO on coordinating surveillance.

A. Dengue epidemiology. Thankfully 2017, like 2016, had a relatively low incidence of dengue in Laos, unlike 2013. We continue to support with diagnostic tests, dengue surveillance for Mahosot Hospital, Luang Nam Tha, Xieng Khouang and Salavan Provincial Hospitals.

We describe the complexity of dengue epidemiology in Laos, demonstrating dynamic circulation that varies over space and time, according to serotype in Castonguay-Vanier *et al.* (2018). We recruited 1,912 consenting patients presenting with WHO dengue criteria at Mahosot Hospital between 2006 and 2010 and 1,413 patients with undifferentiated fever were recruited, between 2008 and 2010, at Luang Namtha Provincial Hospital and 555 at Salavan (SV) Provincial Hospital. Peaks of dengue infection were observed in the rainy seasons. Importantly, 11% of confirmed cases in the provinces and 4.6% in the capital were detected during the dry and cool seasons (between December and February).

All four dengue serotypes were detected among the 867 RT-PCR positive patients: 76.9% dengue-1, 9.6% dengue-2, 7.7% dengue-4 and 5.3% dengue-3. Dengue-1 was the predominant serotype throughout except in Luang Namtha in 2008 and 2009 when it was dengue-2. Phylogenetic analyses of dengue virus envelope sequences suggest concurrent multiple introductions of new strains as well as active dengue circulation throughout Laos and with neighbouring countries. It is therefore of great importance to develop and strengthen a year-round nation-wide surveillance network, with coordination with neighbouring countries, in order to collect data that would allow anticipation of public health issues caused by the occurrence of large dengue outbreaks.

B. Dengue RDTs. We continued the evaluation of the thermal stability of dengue RDTs (see Phommasone *et al.* 2015, in 2015 Annual Report) in tropical temperatures using patient sera strengthening the evidence of the robustness of the NS1 cassette after storage (Sengvilaipaseuth *et al.* 2017).

C. Rapid diagnostic tests for JEV diagnosis. Sengvilaipaseuth *et al.* (2017) evaluated two rapid diagnostic tests (RDTs) for anti-JEV immunoglobulin M (IgM) detection. Consecutive cerebrospinal fluid and serum from 388 patients with suspected JEV infections admitted to six hospitals in Laos were tested with one of two SD-Bioline anti-JEV IgM RDTs and the World Health Organization standard anti-JEV IgM enzyme-linked immunosorbent assay. The performance of both RDTs showed strikingly low sensitivity in comparison to anti-JEV IgM antibody capture ELISA (2.1-51.4%), suggesting low sensitivity of the RDTs. These data suggest that neither RDT are useful for diagnosing JEV infection in Laos.

C. Hand, Foot and Mouth disease. We continue to support enteroviral PCR for surveillance of Hand, Foot and Mouth disease (HFMD) as it is likely that there will be a large outbreak in Laos in the future, as has happened in adjoining countries in the last decade.

E. *Zika virus* infection. With current global concern of the public health impact of this emerging pathogen and possible association of infection with microcephaly, we are working with partners to build diagnostic capacity at Mahosot Hospital. We are expanding the work on PCR detection of *Dengue virus* from RDTs (see above) to detect *Zika virus* and *Chikungunya virus* to facilitate national surveillance of these pathogens, with the Naval Medical Research Center-Asia.

F. JEV patient clinical follow up. Dr Phouvieng Douangdala successfully completed his University of Health Sciences thesis on the disability associated with CNS JEV infection, using the Liverpool Outcome Score. Of all patients assessed, 1/5 died during hospitalization or after discharge. Although the mortality was similar between children and adults, the neurological sequelae were more serious in children. During the ~ 60 months follow up, the proportion of the patients who completely recovered (without neurological sequelae) at the last follow up was 38.3% and this figure was significantly higher in adults (48.9%) than in children (27.7%).

G. Acute Respiratory Illness. The Human Respiratory Syncytial Virus (RSV) causes epidemics of acute respiratory infection (ARI), especially bronchiolitis and pneumonia, in children worldwide. To investigate the RSV burden in Laos, we conducted a one-year study in children <5 years old admitted to Mahosot Hospital to describe clinical and epidemiological characteristics and predictive factors for severity of RSV-associated ARI (Nguyen *et al.* 2017). Pooled nasal and throat swabs were tested using multiplex real-time PCR for 33 respiratory pathogens (FTD® kit). Of 383 patients, 98.4% were positive for at least one microorganism, of which RSV was the most common virus (41.0%), with a peak in the rainy season. Most RSV inpatients had pneumonia (84.1%), of whom 35% had severe pneumonia. Children <3-months old were a high-risk group for severe pneumonia, independently of RSV infection. Our study suggests that RSV infection is frequent in Laos and commonly associated with pneumonia in hospitalized young children. Further investigations are required to provide a better overall view of the Lao nationwide epidemiology and public health burden of RSV infection over time.

H. Rabies. Laos is a rabies-endemic country in which dogs are the main reservoir and continue to present health risks for both human and animals. In a project with the National Animal Health Laboratory, passive, laboratory-based rabies surveillance was performed for suspected cases of dog rabies in Vientiane Capital during 2010-2016 and eight additional provinces between 2015 and 2016 using the Direct Fluorescent Antibody Test (DFAT) (Douangngeun *et al.* 2017). Of 415 dog samples submitted for diagnosis 284 were rabies positive. The majority of cases (257) were from Vientiane Capital. Rabies cases were more common during the dry season. The use of laboratory-based rabies surveillance is a useful method of monitoring rabies in Lao PDR and should be expanded to other provincial centres, particularly where there are active rabies control programmes.

6. One Health

We participate in two One Health projects in addition to the studies above on scrub typhus and leptospirosis. LACANET (http://www.onehealthsea.org/lacanet) is a European Union-funded, binational collaboration between Lao PDR and Cambodia in association with the Wildlife Conservation Society (WCS) and Institut Pasteur- Cambodia to conduct field surveillance of zoonotic diseases at human-wildlife interfaces. COMACROSS (http://www.onehealthsea.org/comacross) is also a EU funded project, led by the Centre de coopération internationale en recherche agronomique pour le développement (CIRAD) and linked to the SEAe project (above). Both projects end in early 2018.

A. Perception of health risk due food sold by vegetable, domestic meat and wildlife vendors in Lao markets. As part of LACANET and her successful IFMT MSc thesis, Dr Chanfong Philavong investigated vendors' perception of health risk due to food sold in markets. Wild and domestic animals are potential carriers of diverse diseases, and may be potential sources of contamination not only to the consumer, the persons who buy meat, but also to the butcher and the vendors. A descriptive cross-sectional study in markets with traders selling wildlife meat was conducted. Every vegetable, domestic meat and wildlife meat vendor in three major markets (one in the north, one in the centre and one in the south) were solicited to participate to the study. In total 177 persons consented, consisting of 85 vegetable vendors, 57 domestic meat_vendors and 35 wildlife meat vendors. Nearly all vendors had a very low perception of risk for health from the food sold. More detailed investigation of these risks and how to engage with market vendors and their customers is needed. This is being written up as a paper.

B. Pathogens in wildlife in markets. Also as part of LACANET, collections of wildlife specimens were made at wildlife trade markets across Laos by the Wildlife Conservation Society. We are testing these samples for the presence of a number of key pathogen species. From January 2015 to October 2017, 717 specimens from 359 animals were sent to LOMWRU for lab analysis. We found that 69 animals contained *Leptospira* spp. and 19 animals contained *Rickettsia* spp., including *R. typhi* and *R. felis.* During the testing process, we also identified samples containing *O. tsutsugamushi*, *L. garvieae*, *Kurthia* spp., *Ehrlichia* spp. TC251-2, *Anaplasma marginale*, *A. phagocytophilum* and *A. bovis*. Our findings suggest that *Leptospira* spp. are the most frequently identified pathogens, of those we tested for, in wildlife trade. The discovery of *R. felis*, an emerging rickettsial pathogen, and *O. tsutsugamushi* are the first reported cases in a squirrel species.

Pallas's, Grey-bellied, and Red-cheeked squirrels were the most common wildlife species sampled in markets.

Our observations indicated their potential as multiple disease reservoirs, with a total of six different pathogen species being identified in squirrels. We received most samples from the markets located in Champasak and Bolikhamxay provinces indicating that these areas may be high volume markets for wildlife trade, with Pha-hom and Thajok serving as possible hotspots for cross transmission. However, the highest positivity rates were found in the samples collected at the Provincial Offices of Forest Inspection (PoFI), especially the Bolikhamxay and Vientiane PoFIs where wildlife were confiscated. Species identification of positive *Leptospira* spp. and *Rickettsia* spp. are in progress to determine whether they are pathogenic strains. We are also investigating the genotype of *O. tsutsugamushi* detected in squirrel samples. We have performed DNA extraction of the ectoparasites collected along with the wildlife samples and they are now being analyzed by PCR as part of the LACANET project.

C. Serology of market vendors to wildlife-borne diseases. Dr Nilandone Senvanpan conducted this study for her IFMT MSc thesis research, to evaluate the immunological status regarding three wildlife and human pathogens (murine typhus, scrub typhus and leptospirosis) in vendors working in Lao markets**.** Consenting fresh food vendors (150) in major Lao markets in Xiengkhouang, Bolikhamxay and Saravan Provinces were asked for blood samples and a series of questions related to their work. The prevalence of anti-leptospiral antibodies was 11% for IgM and 6% for IgG, 3% for IgM and 25% for IgG for anti-murine typhus antibodies, and 7% for IgM and 19% for IgG for anti-scrub typhus antibodies. Sellers of wildlife meat had an increased probability of having anti-scrub typhus IgG. The study is being continued with two more sampling rounds in order to investigate changes in vendor serostatus through time as part of the LACANET project.

D. Perceptions of risks associated with bats. In order to contribute to recommendations improving the management of risks linked to the potential emergence of Nipah and other bat-borne infectious diseases in Laos, we conducted a project to understand better bat-human interactions in the framework of daily activities (agriculture, fruit harvesting, hunting, market chain etc.). This was conducted on the periphery of Vientiane, amongst the general population and amongst palm fruit traders as part of the COMACROSS project.

7. Malaria

A. Malaria diagnosis – positive control wells. Rapid diagnostic tests (RDTs) are widely used for malaria diagnosis, but lack of quality control at point of care restricts confidence in test results. Prototype positive control wells (PCW) containing recombinant malaria antigens have been developed to identify poor-quality RDT lots. We worked with the Foundation for Innovative New Diagnostics to assess community and facility health workers' (HW) ability to use PCWs to detect degraded RDTs in Laos and Uganda (Bell *et al.* 2017). A total of 557 HWs participated in Laos (267) and Uganda (290). After training, most (88% to 99%) participants correctly performed the six key individual PCW steps; performance was generally maintained during the 6-month study period. Nearly all (97%) reported a correct action based on PCW use at routine work sites. PCW availability can improve HWs' confidence in RDT results, and benefit malaria diagnostic programs. These data support the implementation of PCWs in RDTs.

B. Artemisinin-resistance – clinical aspects. With the spread of *Plasmodium falciparum* artemisinin-resistance in Asia there is an urgent need to explore alternative antimalarial treatments, including triple combination artemisinin combination therapies (ACTs). We have participated, with the Centre for Malariology, Parasitology and Entomology, in the multicentre TRAC-2 study, coordinated by MORU-Bangkok, at Sekong Provincial Hospital. This is a randomised clinical trial comparing parasite clearance in uncomplicated falciparum malaria between artemether-lumefantrine and artemether-lumefantrine plus amodiaquine. These data will be useful for informing optimal future ACT Government policy. With the decline in *Plasmodium falciparum* malaria in Laos, patient recruitment has been slow with 11 patients recruited by December 2016 before the trial completed in late 2017.

C. Molecular markers of antimalarial resistance. We have been collecting filter paper blood spots from malaria patients all over southern Laos, where malaria is more prevalent, for the last ten years, with the Centre for Malariology, Parasitology & Entomology, to examine how the frequency of molecular markers of anti-malarial resistance, including those of artemisinin resistance, have changed with the reduction in chloroquine and sulphadoxine-pyrimethamine (SP)

use, in collaboration with the Southwest Foundation for Biomedical Research in Texas and colleagues in MORU-Bangkok, including Professor Mallika Imwong and Dr Olivo Miotto.

Imwong *et al.* (2017) presented some of these data, using molecular genotyping of *P. falciparum* from filter paper blood spots from Myanmar, north-eastern Thailand, southern Laos, and western Cambodia for PfKelch13 mutations and for Pfplasmepsin2 gene amplification. The latter indicates piperaquine resistance. In 2014-15, a single PfKelch13 C580Y haplotype lineage, which emerged in western Cambodia in 2008, was detected in 65 of 88 isolates from north-eastern Thailand, 86 of 111 isolates from southern Laos, and 14 of 14 isolates from western Cambodia. Pfplasmepsin2 amplification was not described from Laos but such parasites were described from NE Thailand samples from 2015, suggesting that this is likely to now be present in Laos. Elimination of falciparum malaria from this region should be accelerated while available antimalarial drugs still remain effective.

D. Glucose-6-phosphate deficiency and malaria. Glucose-6-phosphate deficiency is thought to be common in Laos but the lack of information on the prevalence of different types of deficiency impairs decision making on the use of primaquine in vivax malaria. We have therefore conducted surveys of the prevalence of phenotypic and genotypic markers of G6PD deficiency in Sekong and Salavan Provinces in collaboration with CMPE, SMRU and Institut de Recherche pour le Développement (IRD). A G6PD deficiency survey conducted in six randomly selected villages of two districts of Sekong province demonstrated that, using the Trinity fluorescence spot test, the frequency of people with phenotypic G6PD deficiency was ~ 4% (70/1,897). Molecular G6PD analysis is continuing.

E. Targeted malaria elimination. Recently it has been realised that a significant proportion of apparently well people in rural Asia have *P. falciparum* infections that are not detected by RDTs or microscopy but are evident by high blood volume ultra-sensitive quantitative PCR (uPCR) (see above). With these high frequencies of apparently asymptomatic *P. falciparum,* trials of Targeted Malaria Elimination (TME) with DHA-piperaquine in Nong District, Savannakhet Province, with key public engagement actions, started in 2016 and were completed in late 2017. This is funded by

Assoc Prof Mayfong Mayxay and Dr Koukeo Phommasone with MORU Network team at TME Symposium Antwerp October 2017

the Bill and Melinda Gates Foundation with CMPE and MORU-Bangkok. Dr Koukeo Phommasone, Dr Tiengkham Pongvongsa and Dr Bipin Adhikari are conducting different aspects of this work for their PhD theses.

Three rounds of mass drug administration (DHA-piperaquine) were completed in the two intervention villages and analysis of the comparative epidemiology of *P. falciparum* and *P. vivax* in these communities is continuing. Intensive public engagement programs have been implemented and their impact studied. Adhikari *et al.* (2017a) examined the elements of effective community engagement for mass antimalarial administration in this trial. They concluded that the community engagement strategy that accompanied TME in Laos was successful with high levels of participation in mass anti-malarial administration (>85%). Five key elements were identified: (1) stakeholder and authority engagement, which proceeded from national level, to regional/district and local level; (2) local human resources, particularly the recruitment of local volunteers who were integral to the design and implementation of activities in the study villages; (3) formative research, to rapidly gain insight into the local social and economic context; (4) responsiveness whereby the approach was adapted

according to the needs of the community and their responses to the various study components; and (5) sharing control/leadership with the community in terms of decisions on the organization of TME activities.

In a further paper, Adhikari *et al.* (2017b) explored the reasons for participation in TME through a quantitative survey after the completion of the three rounds of MDA. One consenting participant from each household was interviewed (n=158); 94.9% respondents participated in at least one activity (taking MDA or providing blood sample) and 94.0% respondents took part in the MDA and tested their blood in all three rounds. Characteristics of respondents which were independently associated with completion of three rounds of MDA included: attending TME meetings, knowing that malaria can be diagnosed through blood tests, that all members from household participated, liking all aspects of TME and the perception that TME was important. Hence, a responsive approach to community engagement that includes formative research and the involvement of community members is likely to increase the uptake of the intervention.

F. Vivax malaria treatment. At the same site as the TME study, we started, with CMPE and MORU-Bangkok, a randomised, single-blinded controlled treatment trial of subclinical vivax infections with primaquine in Nong District, Savannakhet Province. This compares dihydroartemisinin-piperaquine therapy plus 14 days of supervised primaquine (7mg/kg total dose) versus dihydroartemisinin-piperaquine therapy plus 14 days placebo not containing primaquine. The primary objective is to determine whether a 14 day course of 0.5 mg/kg/day primaquine can eliminate subclinical *P. vivax* infections detected by high volume ultra-sensitive PCR (uPCR). This study should be completed in May 2018.

8. Intensive Care Medicine

Dr Rebecca Inglis is leading her DPhil mixed methods research in collaboration with Dr Khamsay Detleuxay, Head of Mahosot Hospital Adult Intensive Care Ward, on three ICUs in Laos to investigate the optimal design of a Lao-run ICU training course.

Dr Rebecca (Bex) Inglis and Ms Palingnaphone Koummarasy at the inaugural Lao Critical Care Society Conference in December 2017

9. Dermatology

Dr Cat Wootton is leading a series of projects on the prevalence of skin disease in rural Laos and on contact allergy.

10. Medicine quality & pharmacy

A. The WorldWide Antimalarial Resistance Network (WWARN) & Infectious Disease Data Observatory (IDDO). The WWARN/IDDO Medicine Quality Scientific Group is based at Mahosot Hospital and continues to tabulate and map reports of the quality of antimalarials (see http://www.wwarn.org/resistance/surveyors/antimalarial-quality). WWARN is now within the Infectious Diseases Data Observatory (IDDO; https://www.iddo.org/medicine-quality) and we are expanding this system, with Wellcome Trust support, for other classes of essential medicines as the MAPQAMP project. We are tabulating the accessible data on the quality of maternal health medicines, antibiotics, antidiabetics, anti-retrovirals, anti-tuberculous drugs, and veterinary medicines and are mapping these for release in 2018. They will also be analysed for reviews on the quality of these essential medicines in 2018. We are working with HealthMap (http://www.healthmap.org/en/) on trawling the lay literature in multiple languages for reports of poor

Ms Vayouly Vidhamaly, Dr Serena Vickers, Mr Olay Boupha, Mr Kem Boutsamay and Mr Stephen Zambrzycki - working on the ADB project on evaluation of medicine quality screening devices

quality medicines and using text mining to automate searches.

We are also working with the United States Pharmacopeia to build an individual sample database and mapping system, to include data from the USP MQDB system (see http://apps.usp.org/app/worldwide/medQualityDatabase/terms.html).

B. The unexpected power of toothpicks. Our collaborators Mathew Bernier and Facundo Fernandez of Georgia Institute of Technology in Atlanta, are experimenting with portable and low cost ionization sources for mass spectrometry for analysing medicines, important as mass analyzers become potentially portable. With triboelectric nanogenerators (TENG), the charge required to produce ions needed for sensitive analyte detection can be obtained reproducibly without the need for high voltage electrical circuitry. Experiments performed in this study show that a simple extraction into methanol along with the use of a sliding freestanding (SF)-TENG-powered electrospray from a dry wooden toothpick can provide good detection capabilities, but with much simpler instrumentation.

C. Evaluation of new diagnostic devices. We are working with Global Good, pharmacists at Mahosot Hospital, the Faculty of Pharmacy of the UHS and the Bureau of Food and Drug Inspection of Laos to evaluate the diagnostic accuracy of a small Near-Infrared device for screening tablet quality. We are awaiting the final reference chemistry results before writing this work up.

With funding from the Asian Development Bank we are investigating the comparative diagnostic accuracy and cost-effectiveness of a diversity of portable and handheld medicine quality screening devices. This has proceeded in three phases. In phase 1 we have reviewed the scientific literature published on the diagnostic accuracy and use of these devices. In phase 2, colleagues at Georgia Tech in Atlanta, USA, evaluated the diagnostic accuracy of a wide diversity of devices in the laboratory. In phase 3, we are working with the Bureau of Food and Drug Inspection inspectors to understand their advantages and disadvantages in an evaluation pharmacy we have created. Health economists from MORU in Bangkok also analysed

the cost-effectiveness of the devices compared to the current practice in Laos. The results will be discussed at a meeting in Vientiane on 9th and 10th April 2018.

We also work with Dr Fred Behringer (Surveillent LLC, USA) on FTIR techniques for evaluating the quality of anti-tuberculosis medicines.

D. Falsified diazepam – Democratic Republic of the Congo. We worked with Médecins sans Frontières (MSF), Switzerland, on a large epidemic of dystonic reactions in north-eastern Democratic Republic of the Congo (DRC) (Peyraud *et al.* 2017). Over 1,000 patients developed dystonic reactions after taking 'diazepam' that actually contained large amounts of haloperidol.

E. Guidelines for medicine quality surveys. We have revised the MEDQUARG guidelines (Newton *et al.* 2009) on conducting and reporting surveys for the quality of medicines for the WHO. These have now been formally published as the Guidelines on the Conduct of Surveys of the Quality of Medicines in WHO Technical Report Series, No. 996, 2016, Annex 7 (2016; 36 pages). See:

http://apps.who.int/medicinedocs/en/m/abstract/Js22404en/

The key work of Patricia Tabernero, with Sue Lee, Kasia Stepniewska and Paul Newton, in these guidelines was acknowledged and corrected by WHO in 2017.

F. Forensics. We are working on innovative techniques to look for DNA in falsified medicines and using stable isotope ratios in starch excipients to try to determine the geographical origin of such 'medicines' in comparison to the genuine products. The data are being analysed and will be available in 2018.

G. Packaging. Working with the Institut de la Francophonie pour la Médecine Tropicale (IFMT), we have been surveying the information and language of antimalarial packaging – much of which is in the wrong language for Laos or too small a font to read!

H. Legal and definitions mapping. We have completed a pilot WWARN project to map national laws related to medicine quality and the definitions of different types of poor quality medicines used, funded by INTERPOL.

Ms Vayouly Vidhamaly & Mr Olay Boupha in the Evaluation Pharmacy for the ADB Medicines Screening Devices Project

Dr Phommady Vethsaphong, a Lao neonatologist, discusses antimicrobial resistance at the Vientiane Science Café, University of Health Sciences, in March 2017

I. Access to Medicines Index. The global reporting of poor quality medicines between stakeholders is woeful. We proposed to the Access to Medicines Index (AMI) (http://www.accesstomedicineindex.org/), based in The Netherlands, that they include evaluation of the policies that the pharmaceutical industry have, and their adherence to these, for the rapid reporting of poor quality medicines to national medicine regulatory authorities and the WHO Rapid Alert system. The first inclusion of these data in the AMI were published in 2016 – see: http://accesstomedicineindex.org/media/atmi/Access-to-Medicine-Index-2016.pdf. The methodology is being updated for the next report.

J. Modelling of the impact of poor quality medicines. There is little objective information on the consequences of poor quality medicines on patient outcomes and, for anti-infectives, on drug resistance (Newton *et al.* 2016). We are being funded by the Wellcome Trust to model, with Professors Lisa White and Joel Tarning of MORU-Bangkok, the consequences of poor quality antimalarials, anti-TB drugs and anti-HCV drugs on patient outcome and drug resistance. The initial results will be presented at the Conference on Medicine Quality & Public Health in Oxford in September 2018.

K. Pharmacovigilance & medicine quality. Caillet & Newton (in press) describe the public health issues of poor quality medicines and the factors that facilitate their existence and those that impede action to ensure that patients take good quality medicines. They discuss the role of pharmacovigilance in detecting poor quality medicines. Publication of this book has been delayed.

L. Reporting. If we find any evidence of poor quality medicines in Laos through our work we report these findings as soon as possible to the Food and Drug Department, Government of the Lao PDR.

M. Adverse drug reaction (ADR)-related hospitalizations. The health dangers of medicines of unknown identity (MUIs) (loose pharmaceutical units repackaged in individual bags without labelling of their identity) have been suspected in low- and middle-income countries (L/MICs) (Caillet *et al.* 2017). Using visual and analytical tools to identify MUIs, we investigated the frequency of, and factors associated with, adverse drug reaction (ADR)-related hospitalizations at Mahosot Hospital. MUIs suspected of being involved in ADR(s) were identified through comparison of visual characteristics of tablets/capsules with that of reference medicines and by proton nuclear magnetic resonance and mass spectrometry analyses. The frequency of hospitalizations related to an ADR was 5.1% and 12.8% patients used MUIs in the 2 weeks preceding hospitalization. They were more likely to be hospitalized because of an ADR than patients using medicines of known identity. MUIs were mainly involved in bleeding gastroduodenal ulcers. There is a need to ensure appropriate labelling of medicines at dispensing and to provide well-suited tools to identify MUIs in clinical settings to improve drug safety and patients' care in developing countries with limited capacities for drug analysis.

N. Oral artesunate monotherapy. In 2007 the World Health Assembly (WHA) agreed that oral artemisinin monotherapy (AMT), such as oral artesunate, should no longer be manufactured, produced, or distributed, as important contributors to multi-drug resistant malaria. In some countries strides have been made at reducing their production, use and export. However, work with ACTWatch has demonstrated that it persists in some countries, such as Nigeria (ACTWatch *et al.* 2017a) and Myanmar, with production for export continuing in China, India and Vietnam. AMT has been banned in Nigeria but in 2015 the ACTWatch project nationally representative outlet survey found significant amounts of AMT, primarily oral artesunate, available - highest among pharmacies (84.0%) and Patent Propriety Medicine Vendors (38.7%) but rarely found in the public sector (2.0%). Oral AMT consisted of 2.5% of the national anti-malarial market share. Strategies to effectively halt production and export are needed in Vietnam, China and India.

O. Non-Quality-assured artemisinin combination therapy. The extent to which non quality-assured artemisinin-based combination therapies (non-QAACT) are available and used to treat malaria in endemic countries is poorly documented. ACTWatch Group *et al.* (2017) used national and sub-national medicine outlet surveys conducted in eight study countries (Benin, Democratic Republic of the Congo, DRC (Kinshasa and Kantanga), Kenya, Madagascar, Nigeria, Tanzania, Uganda and Zambia) between 2009 and 2015 to describe the non-QAACT market and to document trends in availability and distribution of non-QAACT in the public and private sector. In 2014/15, non-QAACT were most commonly available in Kinshasa (83%), followed by Katanga (53%), Nigeria (48%), Kenya (42%), and Uganda (33%). Non-QAACT accounted for 20% of the market share in the private sector in Kenya, followed by Benin and Uganda (19%), Nigeria (12%) and Zambia (8%); this figure was 27% in Katanga and 40% in Kinshasa. Public sector non-QAACT availability and distribution was much lower, with the exception of Zambia (availability, 85%; market share, 32%). Addressing the availability and distribution of non-QAACT will require effective private sector engagement and evidence-based strategies to address provider and consumer demand for these products. These efforts may be critical not only to patient health and safety, but also to effective malaria control and protection of artemisinin drug efficacy in the face of spreading resistance.

P. Course on Medicine Quality & Public Health. In July 2017, with Boston University School of Public Health, we ran the annual Course on Medicine Quality & Public Health in Boston, previously held at the London School of Hygiene and Tropical Medicine.

Q. Medicine Quality Side Meetings. We organized, with the United States Pharmacopeia, the annual side meeting on medicine quality at the American Society of Tropical Medicine & Hygiene Conference in Baltimore and led by QUAMED at the European Congress on Tropical Medicine & International Health in Antwerp.

R. World Health Organisation. In November 2017 we presented evidence to the Member State Mechanism for Substandard and Falsified Medicines of WHO in Geneva.

S. Conference on Medicine Quality & Public Health in Oxford in September 2018 (http://www.tropicalmedicine.ox.ac.uk/medicinequality2018/). We are organizing this with the annual Course on Medicine Quality & Public Health in Oxford the week before.

T. Mr Theophilus Ndorbor, WHO/TDR Fellow, is spending 2018 with us, working on West African MRA engagement and reviewing the global evidence on the quality of cardiovascular medicines.

11. Modelling and public health

Under the leadership of Profs Lisa White and Ben Cooper in MORU-Bangkok, a small public health modelling group is developing in Laos, with Drs Rene Niehus, Khansoudaphone Phakhounthong, Phetsavanh Chanthavilay, Olivier Celhay & Tamalee Roberts, working on a series of projects on antimicrobial resistance, malaria epidemiology and typhus antibody responses. A course in Vientiane on modeling and public health policy, run by MORU-Bangkok, is planned for 2018.

Visiting team from Naval Medical Research Center-Asia, Singapore with Microbiology Laboratory team, clockwise from left: Cmdr Fred Stell, Lt Cmdr Jeff Hertz, Capt Patrick Blair, Paul Newton, Matt Robinson, Dr Manivanh Vongsouvath and Lt Rebecca Pavlicek

ENGAGEMENT

A wooden box arrived

Community perceptions and engagement

Now that there are more data on infectious disease epidemiology in Laos, we are conducting public engagement research and implementation with MORU and the University of Health Sciences. This has been a key component of the TME project (above) with intensive work to understand how to optimally engage with people in Laos so that the benefits/risks of different interventions, such as mass drug administration, can be explored and communities can make informed decisions.

A. The Science Café project has continued with sessions on AMR and diabetes with lively discussions on both topics. We plan to hold these every 2 months.

B. E-Library. We have been working with the University of Health Sciences (UHS) to build a page on their website as an e-library – as a repository of published and grey literature information about Lao public health - see: http://uhs-elibrary.la/index.php? If you have any open access papers relevant to public health in Laos please submit them by sending the pdfs to elibrary.uhs@gmail.com. We hope very much that this will become a Lao national resource for health workers and policy makers.

C. Lao Medical Journal. We assist with the publication of the Lao Medical Journal (LMJ), the first Lao language medical journal. Assoc. Professor Mayfong Mayxay is an editor. We hope that the LMJ will be fully bilingual soon. It is freely downloadable on the e-library at UHS. See: http://uhs-elibrary.la/Elibrary.php?&parentID=0&CatID=10

D. LOMWRU website. The LOMWRU aspects of the www.tropmedres.ac website has been updated with more details of LOMWRU PIs. See http://www.tropmedres.ac/lomwru-laos

E. Short Course on Medicine Product Quality & Public Health. We organised the third Course on Medicine Quality and Public Health at the Boston University School of Public Health in July 2017, with support from the Medicines for Malaria Venture. This will move to Oxford University for the 2018 course (see: https://www.conted.ox.ac.uk/courses/quality-of-medical-products-and-public-health#overview) and then hopefully to West Africa.


Inside there was a MALDI-TOF

OTHER ACTIVITIES

F. Medicine Quality. As part of the MAPQAMP project within IDDO we are developing a system for engaging with stakeholders, especially medicine regulatory authorities in LMICs.

G. Pint of Science – this engagement system has started in Thailand (Robinson *et al.* 2017).

A. External quality assurance. We participate in the UK National External Quality Assessment Service (NEQAS) scheme for general bacteriology, antimicrobial susceptibility testing, AAFB microscopy and mycobacterial culture and the WPRO scheme for JEV IgM ELISA QA.

B MOPSOP and Safety liaison. We have multiple links for liaison across the Major Overseas Programme for building consensus on Standard Operating Procedures for laboratory assays and for laboratory safety.

C. Talks etc. The Laboratory runs monthly lunchtime journal clubs, monthly scientific seminars and has frequent talks by academic visitors. LOMWRU has contributed to the monthly scientific talks of Mahosot Hospital and the annual Lao Internal Medicine and Paediatric CME Conferences. We also participate regularly via Webex in seminars at MORU in Bangkok.

D. Pathogen Asset Control System (PACS). With the kind support of DTRA of the USA, LOMWRU, along with other medical organisations in Vientiane, has a new Pathogen Asset Control System (PACS) for the barcoding and cataloguing of samples so that they can be accurately stored and located. The use of this system is being extended through the laboratories.

E. LIMS. With the considerable help of MORU-Bangkok and COMRU, we have installed a Laboratory Information Management System (LIMS) in the Microbiology Laboratory that went live in January 2017 and has already improved the efficiency and accuracy of the microbiological service, and greatly facilitated data retrieval. It will also put us in a good position to act as a sentinel site for the provision of data to the WHO Global Antimicrobial Resistance Surveillance system (GLASS).

F. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF). In November 2017 we were fortunate to receive a MALDI-TOF machine that will be used for identification of otherwise hard to identify pathogens and research on the identification of Lao vectors, especially ticks and which pathogens they carry.

G. Rickettsial Coordination Meetings. The Network holds these every twelve months, organised by Dr Matthew Robinson.

KEY COLLABORATIONS

French Cheese lunch courtesy of Dr Audrey

Within Lao PDR

Centre for Malariology, Parasitology & Entomology, Ministry of Health
National Centre for Laboratory & Epidemiology, Ministry of Health
Department of Communicable Disease Control (DCDC), Ministry of Health
Department of Curative Medicine, Ministry of Health
Food and Drug Department, Ministry of Health
University of Health Sciences, Ministry of Health
Provincial Hospitals of Luang Nam Tha, Xieng Khouang, Salavan and Sekong
Savannakhet Provincial Malaria Station
Mittaphab, Sethathirat, Childrens, Police and Army Hospitals, Vientiane
National Animal Health Laboratory
Bureau of Food and Drug Inspection, Ministry of Health

World Health Organisation Lao Country Office, Vientiane
Institut de la Francophonie pour la Médecine Tropicale
Institut de Recherche pour le Développement
Centre d'Infectiologie Christophe Mérieux du Laos
Institut Pasteur du Laos
Health Frontiers, Vientiane
US CDC, US Embassy
International Water Management Institute

International (in addition to collaborations with MORU, SMRU, COMRU, MOCRU and OUCRU), in alphabetical order of institution

Jayasree Iyer, Danny Edwards, Beth Boyer & Wim Leereveld, Access to Medicine Foundation, Haarlem, The Netherlands

Prof Joost Wiersinga, University of Amsterdam, The Netherlands

Dr Robert Gibbons, Department of Virology, Armed Forces Research Institute of Medical Sciences (AFRIMS), Bangkok, Thailand

Dr Joerg Blessmann, Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany

Professor Richard Laing, Dr Veronika Wirtz and Dr Erin Hasselberg, School of Public Health, Boston University, Boston, USA

Professor Muhammad Zaman, Department of Biomedical Engineering, Boston University, Boston, USA

Dr Mike Green, CDC, Atlanta, Georgia, USA

Dr Serge Morand, CIRAD, Bangkok

Dr Aurelie Binot, CIRAD, France

Professor Sharon Peacock, London School of Hygiene and Tropical Medicine, UK

Professor Adrian Linacre, Flinders University, Australia

Mrs Aline Plançon, FMEDS, Paris, France

Nicola Ranieri, Forensic Chemistry Center, Food & Drug Administration, Cincinnati, Ohio, USA

Professor Facundo Fernandez, Georgia Institute of Technology, Atlanta, Georgia, USA

Dr Jyoti Joshi & Professor Ramanan Laxminarayan, Global Antibiotic Resistance Partnership, Washington DC, USA

Dr Dallas Mildenhall, GNS Science, New Zealand

Dr Mariana Mirabel, Paris Cardiovascular Research Centre, Inserm U970, European Georges Pompidou Hospital, Paris Descartes University, Cardiology Department, European Georges Pompidou Hospital, Paris, France

Prof Anne Roussin, Faculté de Pharmacie, UMR1027 Inserm-Universite Toulouse III, France

Dr Raffaella Ravinetto, QUAMED, Institute of Tropical Medicine, Antwerp, Belgium

Drs Paul Horwood and Didier Menard, Institut Pasteur - Cambodia, Phnom Penh, Cambodia

Professor Marc Lecuit and colleagues, Institut Pasteur, Paris, France

Dr Mathieu Picardeau, Unité de Biologie des Spirochètes, Institut Pasteur, Paris

Dr Alain Pierret, Institut de recherche pour le développement, Laos

Dr Olivier Ribolzi, Géosciences Environnement Toulouse, Université de Toulouse, France

Dr Emma Rochelle-Newall, iEES-Paris, Université Pierre et Marie-Curie, Paris, France

Drs Lesley Chesson and Jim Ehleringer, IsoForensics Inc., and Thure Cerling, University of Utah, USA

Drs Lee Smythe & Scott Craig, Leptospiral Reference Laboratory, Coopers Plains, Australia

Professor David Mabey, Dr Heidi Hopkins, Dr Shunmay Yeung and Dr Harparkash Kaur, London School of Hygiene and Tropical Medicine, London, UK

Dr Martin Cinnamond, GHAP, Geneva, Switzerland

Dr Nicolas Peyraud, Médecins sans Frontières (MSF), Geneva, Switzerland

Prof Bart Currie, Menzies School of Health Research, Australia

Prof Paul Keim and Dr David Wagner, Northern Arizona University, USA

Ms Lorna Cox, Nutritional Biomarker Analysis Laboratory, MRC Nutrition, Cambridge, UK

Dr David Litt, Respiratory and Vaccine Preventable Bacteria Reference Unit, Public Health England, London, UK

Dr SJ Gray, Meningococcal Reference Unit, Public Health England, Manchester, UK

Professor Angela Kearns, Staphylococcus Reference Service, Public Health England, Colindale, UK

Professor Al Richards, Rickettsial Diseases Research Program, Naval Medical Research Center, USA

Dr Wei-Mei Ching, Viral and Rickettsial Diseases Department, Naval Medical Research Center, USA

Captain Patrick Blair & Lt Cmdr Jeff Hertz, Naval Medical Research Centre- Asia, Singapore

Dr Julie Logan, Molecular Identification Services Unit, Public Health England

Professor Ramanan Laxminarayan, Public Health Foundation of India, New Delhi, India

Professor Eric Morgan, Queens University, Belfast

Professor Tim Anderson, Southwest Foundation for Biomedical Research, San Antonio, Texas, USA

Dr Damien Chaussabel, Sidra Medical and Research Center, Qatar

Professor David Relman & Dr Stephen Popper, Department of Microbiology and Immunology, Stanford University, California, USA

Dr Fred Behringer, Surveillant LLC, Old Lyme, USA

Professor Daniel Paris, Dr Esther Kuenzli, Dr Rosalie Zimmermann, Dr Jakob Zopfi and colleagues, Swiss Tropical and Public Health Institute, Basel/University of Basel

Dr Tim Barkham, Tan Tock Seng Hospital, Singapore

Dr Souly Phanouvong, Dr Jude Nwokike, Dr Lukas Roth, Dr Victor Pribluda & Dr Mustapha Hajjou, United States Pharmacopeia, Rockville, Virginia, USA

Dr Todd French and Philip Bulterys, University of California-Los Angeles, USA

Dr Daniel Parker, University of California-Irvine, USA

Professor William Horsnell, University of Cape Town

Dr Francis Anto, University of Ghana

Prof Ivo Steinmetz, University of Graz, Austria

Dr Steve Sait, University of Leeds

Professor KT Wong, Faculty of Medicine, University of Malaya, Malaysia

Professor Xavier Nicolas de Lamballerie, UMR «Unité des Virus Emergents» (UVE: Aix-Marseille university - IRD 190 - Inserm 1207 – IHU Méditerranée Infection), Marseille, France.

GCP trainers, Zöe Doran and Jaruwan Tubprasert, with attendees at the GCP Course at Mahosot Hospital December 2017

Professors Didier Raoult, Pierre-Edouard Fournier, Jean-Marc Rolain, Philippe Parola, Rickettsial Reference Laboratory, Aix-Marseille University, France

Dr Fiona Russell and Prof Kim Mullholland, Murdoch Childrens Research Institute (MCRI), University of Melbourne, Victoria, Australia

Dr Andrew Steer and Pierre Smeesters, Murdoch Childrens Research Institute (MCRI), University of Melbourne, Victoria, Australia

Professor Marya Lieberman, Department of Chemistry and Biochemistry, University of Notre Dame, USA

Professor Amir Attaran, Faculties of Law and Medicine, University of Ottawa, Ontario, Canada

Professor John Crump, University of Otago, New Zealand

Professor Nicole Zitzmann & Dr Bevin Gangadharan Department of Biochemistry, University of Oxford, UK

Dr Nicole Stoesser and Professor Derrick Crook, Nuffield Department of Medicine, University of Oxford, UK

Professor Philippe Guérin and the Infectious Diseases Data Observatory, Centre for Tropical Medicine & Global Health, University of Oxford, UK

Dr Rory Bowden and Dr Liz Batty, Wellcome Trust Centre for Human Genetics, University of Oxford

Dr Catherine Moyes, Big Data Institute, University of Oxford

Drs David AuCoin, Paul Brett and Mary Burtnick, University of Nevada School of Medicine, Reno, Nevada, USA

Dr Aleisha Brock and Prof Adrian Esterman, University of South Australia, Adelaide, Australia

Dr Richard Malik, University of Sydney

Professor Albert Ko, Yale School of Public Health, USA

Michael Deats, Pernette Bourdillon-Esteves & Diana Lee, WHO, Geneva, Switzerland

Dr Mathieu Pruvot & Khonsy Khammavong, Wildlife Conservation Society, Asia

TITLES AND ABSTRACTS OF PAPERS PUBLISHED OR IN PRESS 2017

In alphabetical order by first author. If the paper does not include an abstract a brief summary is given in [ ].

1. ACTwatch Group, Ujuju C, Anyanti J, Newton PN, Ntadom G. Collaborators: Akulayi L, Alum A, Andrada A, Archer J, Arogundade ED, Auko E, Badru AR, Bates K, Bouanchaud P, Bruce M, Bruxvoort K, Buyungo P, Camilleri A, Carter ED, Chapman S, Charman N, Chavasse D, Cyr R, Duff K, Guedegbe G, Esch K, Evance I, Fulton A, Gataaka H, Haslam T, Harris E, Hong C, Hurley C, Isenhower W, Kaabunga E, Kaaya BD, Kabui E, Kangwana B, Kapata L, Kaula H, Kigo G, Kyomuhangi I, Lailari A, LeFevre S, Littrell M, Martin G, Michael D, Monroe E, Mpanya G, Mpasela F, Mulama F, Musuva A, Ngigi J, Ngoma E, Norman M, Nyauchi B, O'Connell KA, Ochieng C, Ogada E, Ongwenyi L, Orford R, Phanalasy S, Poyer S, Rahariniaina J, Raharinjatovo J, Razafindralambo L, Razakamiadana S, Riley C, Rodgers J, Rusk A, Shewchuk T, Sensalire S, Smith J, Sochea P, Solomon T, Sudoi R, Tassiba ME, Thanel K, Thompson R, Toda M, Ujuju C, Valensi MA, Vasireddy V, Whitman CB, Zinsou C (2017a) When it just won't go away: oral artemisinin monotherapy in Nigeria, threatening lives, threatening progress. *Malaria Journal.* 16(1):489. doi: 10.1186/s12936-017-2102-7.

Abstract. BACKGROUND: Oral artemisinin monotherapy (AMT), an important contributor to multi-drug resistant malaria, has been banned in Nigeria. While oral AMT has scarcely been found for several years now in other malaria-endemic countries, availability has persisted in Nigeria's private sector. In 2015, the ACTwatch project conducted a nationally representative outlet survey. Results from the outlet survey show the extent to which oral AMT prevails in Nigeria's anti-malarial market, and provide key product information to guide strategies for removal. RESULTS: Between August 10th and October 3rd, 2015 a total of 13,480 outlets were screened for availability of anti-malarials and/or malaria blood testing services. Among the 3624 anti-malarial outlets, 33,539 anti-malarial products were audited, of which 1740 were oral AMT products, primarily artesunate (n = 1731). Oral AMT was imported from three different countries (Vietnam, China and India), representing six different manufacturers and 11 different brands. Availability of oral AMT was highest among pharmacies (84.0%) and Patent Propriety Medicine Vendors (drug stores, PPMVs) (38.7%), and rarely found in the public sector (2.0%). Oral AMT consisted of 2.5% of the national anti-malarial market share. Of all oral AMT sold or distributed, 52.3% of the market share comprised of a Vietnamese product, Artesunat®, manufactured by Mekophar Chemical Pharmaceutical Joint Stock Company. A further 35.1% of the market share were products from China, produced by three different manufacturers and 12.5% were from India by one manufacturer, Medrel Pharmaceuticals. Most of the oral AMT was distributed by PPMVs accounting for 82.2% of the oral AMT market share. The median price for a package of artesunate ($1.78) was slightly more expensive than the price of quality-assured (QA) artemether lumefantrine (AL) for an adult ($1.52). The median price for a package of artesunate suspension ($2.54) was three times more expensive than the price of a package of QA AL for a child ($0.76). CONCLUSION: Oral AMT is commonly available in Nigeria's private sector. Cessation of oral AMT registration and enforcement of the oral AMT ban for removal from the private sector are needed in Nigeria. Strategies to effectively halt production and export are needed in Vietnam, China and India.

Jennifer Boss, Tara Black, Viengmala Sihalath, Sengmany Symanivong in a tuk tuk at Vang Vieng

2. ACTWatch Group, Newton PN, Hanson K, Goodman C (2017b) Do anti-malarials in Africa meet quality standards? The market penetration of non quality-assured artemisinin combination therapy in eight African countries. *Malaria Journal.* 16(1):204. doi: 10.1186/s12936-017-1818-8.

New Year in the Microbiology Laboratory, Dec 2017

Abstract. BACKGROUND: Quality of artemisinin-based combination therapy (ACT) is important for ensuring malaria parasite clearance and protecting the efficacy of artemisinin-based therapies. The extent to which non quality-assured ACT (non-QAACT), or those not granted global regulatory approval, are available and used to treat malaria in endemic countries is poorly documented. This paper uses national and sub-national medicine outlet surveys conducted in eight study countries (Benin, Kinshasa and Kantanga [Democratic Republic of the Congo, DRC], Kenya, Madagascar, Nigeria, Tanzania, Uganda and Zambia) between 2009 and 2015 to describe the non-QAACT market and to document trends in availability and distribution of non-QAACT in the public and private sector. RESULTS: In 2014/15, non-QAACT were most commonly available in Kinshasa (83%), followed by Katanga (53%), Nigeria (48%), Kenya (42%), and Uganda (33%). Non-QAACT accounted for 20% of the market share in the private sector in Kenya, followed by Benin and Uganda (19%), Nigeria (12%) and Zambia (8%); this figure was 27% in Katanga and 40% in Kinshasa. Public sector non-QAACT availability and distribution was much lower, with the exception of Zambia (availability, 85%; market share, 32%). Diverse generics and formulations were available, but non-QAACT were most commonly artemether-lumefantrine (AL) or dihydroartemisinin-piperaquine (DHA PPQ), in tablet formulation, imported, and distributed in urban areas at either pharmacies or drug stores. The number of unique manufacturers supplying non-QAACT to each country ranged from 9 in Uganda to 92 in Nigeria. CONCLUSIONS: Addressing the availability and distribution of non-QAACT will require effective private sector engagement and evidence-based strategies to address provider and consumer demand for these products. Given the variation in non-QAACT markets observed across the eight study countries, active efforts to limit registration, importation and distribution of non-QAACT must be tailored to the country context, and will involve addressing complex and challenging aspects of medicine registration, private sector pharmaceutical regulation, local manufacturing and drug importation. These efforts may be critical not only to patient health and safety, but also to effective malaria control and protection of artemisinin drug efficacy in the face of spreading resistance.

3. Adhikari B, Phommasone K, Pongvongsa T, Kommarasy P, Soundala X, Henriques G, White NJ, Day NPJ, Dondorp AM, von Seidlein L, Cheah PY, Pell C, Mayxay M (2017b) Factors associated with population coverage of targeted malaria elimination (TME) in southern Savannakhet Province, Lao PDR. *Malaria Journal.* 16(1):424. doi: 10.1186/s12936-017-2070-y.

Abstract. BACKGROUND: Targeted malaria elimination (TME) in Lao PDR (Laos) included three rounds of mass drug administrations (MDA) against malaria followed by quarterly blood surveys in two villages in Nong District at Savannakhet Province. The success of MDA largely depends upon the efficacy of the anti-malarial drug regimen, local malaria epidemiology and the population coverage. In order to explore the reasons for participation in TME, a quantitative survey was conducted after the completion of the three rounds of MDA. METHODS: The survey was conducted in two villages with a total of 158 households in July and August 2016. Among the 973 villagers eligible for participation in the MDA, 158 (16.2%) adults (> 18 years) were selected, one each from every household for the interviews using a quantitative questionnaire. RESULTS: 150/158 (94.9%) respondents participated at least in one activity (taking medicine or testing their blood) of TME. 141/150 (94.0%) respondents took part in the MDA and tested their blood in all three rounds. 17/158 (10.7%) were partial or non-participants in three rounds of MDA. Characteristics of respondents which were independently associated with completion of three rounds of MDA included: attending TME meetings [AOR = 12.0 (95% CI 1.1-20.5) (p = 0.03)], knowing that malaria can be diagnosed through blood tests [AOR = 5.6 (95% CI 1.0-32.3) (p = 0.05)], all members from household participated [AOR = 4.2 (95% CI 1.3-14.0) (p = 0.02)], liking all aspects of TME [AOR = 17.2 (95% CI 1.6-177.9) (p = 0.02)] and the perception that TME was important [AOR = 14.9 (95% CI 1.3-171.2) (p = 0.03)]. CONCLUSION: Complete participation in TME was significantly associated with participation in community engagement activities, knowledge that the blood tests were for malaria diagnosis, family members' participation at TME and perceptions that TME was worthwhile. A responsive approach to community engagement that includes formative research and the involvement of community members may increase the uptake of the intervention.

4. Adhikari B, Pell C, Phommasone K, Soundala X, Kommarasy P, Pongvongsa T, Henriques G, Day NPJ, Mayxay M, Cheah PY (2017a) Elements of effective community engagement: lessons from a targeted malaria elimination study in Lao PDR (Laos). *Global Health Action.* 10(1):1366136. doi: 10.1080/16549716.2017.1366136.

Abstract. BACKGROUND: Mass drug (antimalarial) administration (MDA) is currently under study in Southeast Asia as part of a package of interventions referred to as targeted malaria elimination (TME). This intervention relies on effective community engagement that promotes uptake and adherence in target communities (above 80%). OBJECTIVE: Based on the experienced of designing and implementing the community engagement for TME in Laos, in this article we aim to present the elements of effective community engagement for mass antimalarial administration. METHODS: The design and implementation of community engagement, which took place from September 2015 to August 2016 was recorded as field notes, meeting minutes and photographs. These data underwent qualitative content analysis. RESULTS: The community engagement strategy that accompanied TME in Laos was successful in terms of contributing to high levels of participation in mass anti-malarial administration (above 85%). Based on the experience of designing and implementing the community engagement, five key elements were identified: (1) stakeholder and authority engagement, which proceeded from national level, to regional/district and local level; (2) local human resources, particularly the recruitment of local volunteers who were integral to the design and implementation of activities in the study villages; (3) formative research, to rapidly gain insight into the local social and economic context; (4) responsiveness whereby the approach was adapted according to the needs of the community and their responses to the various study components; and (5) sharing control/leadership with the community in terms of decisions on the organization of TME activities. CONCLUSIONS: The community engagement that accompanied TME in Laos had to deal with challenges of implementing a complex study in remote and linguistically isolated villages. Despite these challenges, the study recorded high population coverage. Lessons learnt from this experience are useful for studies and intervention programs in diverse contexts.

5. Ashley E, Recht J, Chua A, Dance D, Dhorda M, Thomas N, Ranganathan N, Turner P, Guerin P, White N, Day, Nicholas D (in press) An inventory of supranational antimicrobial resistance surveillance networks involving low- and middle-income countries since 2000. *J Antimicrobial Chemo.*

Abstract. Low- and middle-income countries

(LMICs) shoulder the bulk of the global burden of infectious diseases and drug resistance. We searched for supranational networks performing AMR surveillance in LMICs and assessed their organisation, methodology, impacts and challenges. Since 2000, 72 supranational networks for AMR surveillance in bacteria, fungi, HIV, TB and malaria have been created which have involved LMICs, of which 34 are ongoing. The median [range] duration of the networks was 6 years [1-70] and number of LMICs included was 7 [1-67]. Networks were categorised as WHO/governmental (n=26), academic (n=24), or pharma initiated (n=22). Funding sources varied, with 30 networks receiving public or WHO funding, 25 corporate, 13 trust or foundation, and four funded from more than one source. The leading global programmes for drug resistance surveillance in tuberculosis, malaria and HIV gather data in LMICs through periodic active surveillance efforts or combined active and passive approaches. The biggest challenges faced by these networks has been achieving high coverage across LMICs and complying with the recommended frequency of reporting.
Obtaining high quality, representative surveillance data in LMICs is challenging. Antibiotic resistance surveillance requires a level of laboratory infrastructure and training which is not widely available in LMICs. The nascent Global Antimicrobial Resistance Surveillance System (GLASS) aims to build up passive surveillance in all member states. Past experience suggests complementary active approaches may be needed in many LMICs if representative, clinically relevant, meaningful data are to be obtained. Maintaining an up-to-date registry of networks would promote a more coordinated approach to surveillance.

6. Ataide R, Ashley EA, Powell R, Chan JA, Malloy MJ, O'Flaherty K, Takashima E, Langer C, Tsuboi T, Dondorp AM, Day NP, Dhorda M, Fairhurst RM, Lim P, Amaratunga C, Pukrittayakamee S, Hien TT, Htut Y, Mayxay M, Faiz MA, Beeson JG, Nosten F, Simpson JA, White NJ, Fowkes FJ (2017) Host immunity to *Plasmodium falciparum* and the assessment of emerging artemisinin resistance in a multinational cohort. Proc Natl Acad Sci U S A. 114(13):3515-3520

Abstract. Artemisinin-resistant falciparum malaria, defined by a slow-clearance phenotype and the presence of *kelch13* mutants, has emerged in the Greater Mekong Subregion. Naturally acquired immunity to malaria clears parasites independent of antimalarial drugs. We hypothesized that between- and within-population variations in host immunity influence parasite clearance after artemisinin treatment and the interpretation of emerging artemisinin resistance. Antibodies specific to 12 *Plasmodium falciparum* sporozoite and blood-stage antigens were determined in 959 patients (from 11 sites in Southeast Asia) participating in a multinational cohort study assessing parasite clearance half-life ($PCt_{1/2}$) after artesunate treatment and *kelch13* mutations. Linear mixed-effects modeling of pooled individual patient data assessed the association between antibody responses and $PCt_{1/2}$. *P. falciparum* antibodies were lowest in areas where the prevalence of *kelch13* mutations and slow $PCt_{1/2}$ were highest [Spearman **ρ** = -0.90 (95% confidence interval, -0.97, -0.65), and Spearman **ρ** = -0.94 (95% confidence interval, -0.98, -0.77), respectively]. *P. falciparum* antibodies were associated with faster $PCt_{1/2}$ (mean difference in $PCt_{1/2}$ according to seropositivity, -0.16 to -0.65 h, depending on antigen); antibodies have a greater effect on the clearance of *kelch13* mutant compared with wild-type parasites (mean difference in $PCt_{1/2}$ according to seropositivity, -0.22 to -0.61 h faster in *kelch13* mutants compared with wild-type parasites). Naturally acquired immunity accelerates the clearance of artemisinin-resistant parasites in patients with falciparum malaria and may confound the current working definition of artemisinin resistance. Immunity may also play an important role in the emergence and transmission potential of artemisinin-resistant parasites.

Khao Lam, Pakse

7. Bell D, Bwanika JB, Cunningham J, Gatton M, González IJ, Hopkins H, Kibira SP, Kyabayinze DJ, Mayxay M, Ndawula B, Newton PN, Phommasone K, Streat E, Umlauf R, Malaria RDT Positive Control Well Field Study Group (2017) Prototype Positive

Control Wells for Malaria Rapid Diagnostic Tests: Prospective Evaluation of Implementation Among Health Workers in Lao People's Democratic Republic and Uganda. *Am J Trop Med Hyg*. 96(2):319-329. doi: 10.4269/ajtmh.16-0498.

Abstract. Rapid diagnostic tests (RDTs) are widely used for malaria diagnosis, but lack of quality control at point of care restricts trust in test results. Prototype positive control wells (PCW) containing recombinant malaria antigens have been developed to identify poor-quality RDT lots. This study assessed community and facility health workers' (HW) ability to use PCWs to detect degraded RDTs, the impact of PCW availability on RDT use and prescribing, and preferred strategies for implementation in Lao People's Democratic Republic (Laos) and Uganda. A total of 557 HWs participated in Laos (267) and Uganda (290). After training, most (88% to ≥ 99%) participants correctly performed the six key individual PCW steps; performance was generally maintained during the 6-month study period. Nearly all (97%) reported a correct action based on PCW use at routine work sites. In Uganda, where data for 127,775 individual patients were available, PCW introduction in health facilities was followed by a decrease in antimalarial prescribing for RDT-negative patients ≥ 5 years of age (4.7-1.9%); among community-based HWs, the decrease was 12.2% ($P < 0.05$) for all patients. Qualitative data revealed PCWs as a way to confirm RDT quality and restore confidence in RDT results. HWs in malaria-endemic areas are able to use prototype PCWs for quality control of malaria RDTs. PCW availability can improve HWs' confidence in RDT results, and benefit malaria diagnostic programs. Lessons learned from this study may be valuable for introduction of other point-of-care diagnostic and quality-control tools. Future work should evaluate longer term impacts of PCWs on patient management.

8. Bharucha T, Vickers S, Ming D, Lee SJ, Dubot-Peres A, de Lamballerie X, Newton PN (*in press*) Association between Reported Aetiology of Central Nervous System Infections and the Speciality of Study Investigators - A Bias Compartment Syndrome? *Trans Royal Soc Trop Med Hyg.*

Abstract. Background: Conventional descriptions of central nervous system (CNS) infections are variably categorised into clinical syndromes for patient investigation, management and research. Aetiologies of the most commonly recognised syndromes, encephalitis and meningitis, tend to be attributed predominantly to viruses and bacteria, respectively. Methods: A systematic review was performed of aetiological studies of CNS syndromes, and data extracted on reported author specialities. Results: The analysis identified an association between the author's speciality and the CNS syndrome studied, with a tendency for virologists to study encephalitis, and microbiologists to study meningitis. Discussion: We suggest there is bias in study design. Stronger multidisciplinary collaboration in CNS infection research is needed.

9. Bonell A, Lubell Y, Newton PN, Crump JA, Paris DH (2017) Estimating the burden of scrub typhus: A systematic review. *PLoS Negl Trop Dis.* 25;11(9):e0005838.

Abstract. BACKGROUND: Scrub typhus is a vector-borne zoonotic disease that can be life-threatening. There are no licensed vaccines, or vector control efforts in place. Despite increasing awareness in endemic regions, the public health burden and global distribution of scrub typhus remains poorly known. METHODS: We systematically reviewed all literature from public health records, fever studies and reports available on the Ovid MEDLINE, Embase Classic + Embase and EconLit databases, to estimate the burden of scrub typhus since the year 2000. FINDINGS: In prospective fever studies from Asia, scrub typhus is a leading cause of treatable non-malarial febrile illness. Sero-epidemiological data also suggest that *Orientia tsutsugamushi* infection is common across Asia, with seroprevalence ranging from 9.3%-27.9% (median 22.2% IQR 18.6-25.7). A substantial apparent rise in minimum disease incidence (median 4.6/100,000/10 years, highest in China with 11.2/100,000/10 years) was reported through passive national surveillance systems in South Korea, Japan, China, and Thailand. Case fatality risks from areas of reduced drug-susceptibility are reported at 12.2% and 13.6% for South India and northern Thailand, respectively. Mortality reports vary widely around a median mortality of 6.0% for untreated and 1.4% for treated scrub typhus. Limited evidence suggests high mortality in complicated scrub typhus with CNS involvement (13.6% mortality), multi-organ dysfunction (24.1%) and high pregnancy miscarriage rates with poor neonatal outcomes. INTERPRETATION: Scrub typhus appears to be a truly neglected tropical disease mainly affecting rural

populations, but increasingly also metropolitan areas. Rising minimum incidence rates have been reported over the past 8-10 years from countries with an established surveillance system. A wider distribution of scrub typhus beyond Asia is likely, based on reports from South America and Africa. Unfortunately, the quality and quantity of the available data on scrub typhus epidemiology is currently too limited for any economical, mathematical modeling or mapping approaches.

10. Caillet C, Sichanh C, Assemat G, Malet-Martino M, Sommet A, Bagheri H, Sengxeu N, Mongkhonmath N, Mayxay M, Syhakhang L, Lapeyre-Mestre M, Newton PN, Roussin A (2017) Role of Medicines of Unknown Identity in Adverse Drug Reaction-Related Hospitalizations in Developing Countries: Evidence from a Cross-Sectional Study in a Teaching Hospital in the Lao People's Democratic Republic. *Drug Saf.* 40(9):809-821.

Abstract. INTRODUCTION: The health dangers of medicines of unknown identity (MUIs) [loose pharmaceutical units repackaged in individual bags without labelling of their identity] have been suspected in L/MICs. Using visual and analytical tools to identify MUIs, we investigated the frequency of, and factors associated with, adverse drug reaction (ADR)-related hospitalizations in a central hospital in Vientiane Capital, Lao People's Democratic Republic (PDR). METHODS: All unplanned admissions, except for acute trauma and intentional overdose, were prospectively recorded during a 7-week period in 2013, leading to include 453 adults hospitalized for ≥24 h. The patients or their relatives were interviewed to complete the study questionnaire. MUIs suspected of being involved in ADR(s) were identified through comparison of visual characteristics of tablets/capsules with that of reference medicines (photograph tool), and by proton nuclear magnetic resonance and mass spectrometry analyses. Factors associated with ADRs were identified by multivariate logistic regression. RESULTS: The frequency of hospitalizations related to an ADR was 5.1% (23/453, 95% confidence interval [CI] 3.1-7.1). Forty-eight (12.8%) patients used MUI(s) in the last 2 weeks preceding hospitalization. They were more likely to be hospitalized because of an ADR (adjusted odds ratio 4.5, 95% CI 1.7-11.5) than patients using medicines of known identity. MUIs were mainly involved in bleeding gastroduodenal ulcers. The photograph tool led to the misidentifications because of look-alike pharmaceutical units in the medicines photograph collection. CONCLUSION: According to the results of this study, there is a need to ensure appropriate labelling of medicines at dispensing and to provide well-suited tools to identify MUIs in clinical settings to improve drug safety and patients' care in developing countries with limited capacities for drug analysis.

11. Caillet C & Newton PN (in press) The case of falsified and substandard medicines in resource-limited countries. IN: Special Issues in Pharmacovigilance in Resource-Limited Countries, edited by Syed Rizwanuddin Ahmad, Springer.

Abstract. Poor quality medicines have been described as a global pandemic that threatens the lives of millions of people. The problem is much more severe in poor-resource countries where pharmaceutical legislation and regulation are limited. Medicines may be of poor quality if they are falsified, substandard or degraded. Few objective data on their prevalence exist but surveys suggest that an alarming proportion of anti-infectives in much of the developing world are of poor quality. The use of poor quality medicines may lead to severe complications not just for the individual but also for the community. Falsified, substandard or degraded drugs with subtherapeutic concentrations of the active ingredient or the wrong active ingredient are likely to engender the emergence and spread of resistance to anti-infectives, putting affordable treatments at risk. Those with excessive amounts of active ingredient or containing wrong harmful active ingredients may induce adverse drug reactions. Furthermore, poor quality medicines lead to a loss of faith of the patients in essential medicines and in health systems. To detect poor quality medicines at different levels of the pharmaceutical supply chain, different techniques have been developed, each with advantages and limits. This chapter describes these aspects of poor quality medicines and also discusses the factors that facilitate their existence and those that impede action to ensure that patients take good quality medicines. We discuss the role of pharmacovigilance in detecting poor quality medicines.

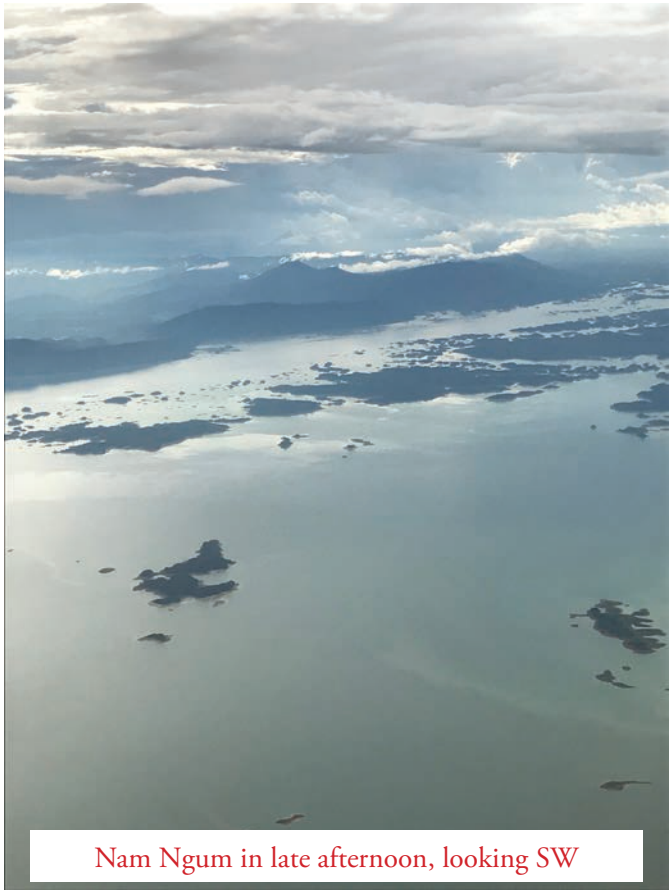
12. Castonguay-Vanier J, Klitting R, Sengvilaipaseuth O, Piorkowski G, Baronti C, Sibounheuang B, Vongsouvath M, Chanthongthip A, Thongpaseuth S, Mayxay M, Phommasone K, Douangdala P, Inthalath S, Souvannasing P, Newton PN, de Lamballerie X,

Dubot-Pérès A (2018) Molecular epidemiology of dengue viruses in three provinces of Lao PDR, 2006-2010. *PLoS Negl Trop Dis.* 12(1):e0006203.

Abstract. Few data on dengue epidemiology are available for Lao PDR. Here, we provide information on the complexity of dengue epidemiology in the country, demonstrating dynamic circulation that varies over space and time, according to serotype. We recruited 1,912 consenting patients presenting with WHO dengue criteria at Mahosot Hospital, Vientiane (central Laos), between 2006 and 2010. Between 2008 and 2010, 1,413 patients with undifferentiated fever were also recruited at Luang Namtha (LNT) Provincial Hospital (northern Laos) and 555 at Salavan (SV) Provincial Hospital (southern Laos). We report significant variations in Dengue virus (DENV) circulation between the three sites. Peaks of DENV infection were observed in the rainy seasons, although 11% of confirmed cases in the provinces and 4.6% in the capital were detected during the dry and cool seasons (between December and February). Four DENV serotypes were detected among the 867 RT-PCR positive patients: 76.9% DENV-1, 9.6% DENV-2, 7.7% DENV-4 and 5.3% DENV-3. DENV-1 was the predominant serotype throughout the study except in LNT in 2008 and 2009 when it was DENV-2. Before July 2009, DENV-2 was not detected in SV and only rarely detected in Vientiane. DENV-3 and DENV-4 were commonly detected in Vientiane, before 2008 for DENV-4 and after 2009 for DENV-3. The phylogenetic analyses of DENV envelope sequences suggest concurrent multiple introductions of new strains as well as active DENV circulation throughout Laos and with neighboring countries. It is therefore of great importance to develop and strengthen a year-round nation-wide surveillance network in order to collect data that would allow anticipation of public health issues caused by the occurrence of large dengue outbreaks.

13. Chansamouth V, McGready R, Chommanam D, Homsombath S, Mayxay M, Newton PN (2017) Enrolling pregnant women in research: ethical challenges encountered in Lao PDR (Laos). *Reproductive Health*. 4 (Suppl 3):167.

Abstract. Laos has the highest maternal mortality ratio in mainland Southeast Asia but there has been little research conducted with pregnant women. We aim to discuss ethical challenges in enrolling pregnant women in research as a part of large pregnancy cohort study in Laos. From 2013 to 2015, a prospective cohort study was conducted with 1000 pregnant women in a rural area of Vientiane, Laos, to determine whether fevers were associated with maternal morbidity and small for gestational age. Incidence of fever was 10% and incidence of small for gestational age was 12%. Level of education, cultural norms about family decision-making, and misconceptions about healthcare during pregnancy were three common issues encountered in enrolling pregnant women to this study. Only 47% of recruited women had completed primary school with no further education, which could affect the decisions women make to participate and remain in the study. Family decision-making is common in Laos; in some cases, we could not recruit pregnant women without agreement from their families. In Laos, many pregnant women and their families had strong beliefs in travelling during late pregnancy or losing small amount of blood (giving ~5 ml blood sample) could negatively impact their pregnancies. These misconceptions affected not only the quality of the study but also the women's opportunities to access healthcare. Good engagement between the research team and study participants, and the provision of more health information to the community, were essential to reducing issues experienced in enrolling pregnant women in this study.



Nam Ngum in late afternoon, looking SW

14. Cheong E, Roberts T, Rattanavong S, Riley TV, Newton PN, Dance DAB (2017) *Clostridium difficile* infection in the Lao People›s Democratic Republic: first isolation and review of the literature. *BMC Infectious Diseases*. 17:635.

Abstract. BACKGROUND: Current knowledge of the epidemiology of *Clostridium difficile* infection in Asia, and in particular the Greater Mekong Subregion, is very limited. Only a few studies from Thailand and Vietnam have been reported from the region with variable testing methods and results, and no studies from Lao People's Democratic Republic (PDR). Therefore we investigated the presence of *C. difficile* in a single centre in the Lao PDR and determined the ribotypes present. METHOD: Seventy unformed stool samples from hospital inpatients at Mahosot Hospital, Vientiane, were tested for the presence of *C. difficile* using selective differential agar and confirmed by latex agglutination. *C. difficile* isolates were further characterised by ribotyping and toxin gene detection. RESULTS: *C. difficile* was isolated from five of the 70 patients, and five different ribotypes were identified (014, 017, 020, QX 107 and QX 574). CONCLUSION: This is the first isolation of *C. difficile* from human stool samples in the Lao PDR. These results will add to the limited amount of data on *C. difficile* in the region. In addition, we hope this information will alert clinicians to the presence of *C. difficile* in the country and will help inform future investigations into the epidemiology and diagnosis of *C. difficile* in Lao PDR.

15. Chewapreecha C, Holden MT, Vehkala M, Välimäki N, Yang Z, Harris SR, Mather AE, Tuanyok A, De Smet B, Le Hello S, Bizet C, Mayo M, Wuthiekanun V, Limmathurotsakul D, Phetsouvanh R, Spratt BG, Corander J, Keim P, Dougan G, Dance DA, Currie BJ, Parkhill J, Peacock SJ (2017) Global and regional dissemination and evolution of *Burkholderia pseudomallei*. *Nat Microbiol*. 2:16263.

Abstract. The environmental bacterium *Burkholderia pseudomallei* causes an estimated 165,000 cases of human melioidosis per year worldwide and is also classified as a biothreat agent. We used whole genome sequences of 469 *B. pseudomallei* isolates from 30 countries collected over 79 years to explore its geographic transmission. Our data point to Australia as an early reservoir, with transmission to Southeast Asia followed by onward transmission to South Asia and East Asia. Repeated reintroductions were observed within the Malay Peninsula and between countries bordered by the Mekong River. Our data support an African origin of the Central and South American isolates with introduction of *B. pseudomallei* into the Americas between 1650 and 1850, providing a temporal link with the slave trade. We also identified geographically distinct genes/variants in Australasian or Southeast Asian isolates alone, with virulence-associated genes being among those over-represented. This provides a potential explanation for clinical manifestations of melioidosis that are geographically restricted.

16. Crump JA, Newton PN, Baird SJ, Lubell Y (2017) Febrile Illness in Adolescents and Adults. Chapter 14. In: Holmes KK, Bertozzi S, Bloom BR, Jha P. DCP Major Infectious Diseases. 3rd ed.

[A review of what we know and the gaps in our knowledge of the aetiology and impact of diverse fevers in adolescents and adults in the tropics]

17. Dance DAB, Limmathurotsakul D, Currie, BJ (2017) *Burkholderia pseudomallei*: challenges for the clinical microbiology laboratory - a response from the front line. *Journal of Clinical Microbiology*. 55(3):980-982. doi: 10.1128/JCM.02378-16.

[Letter in response to a minireview contrasting the US perspective on melioidosis with that in endemic areas]

18. Darton TC, Tuyen HT, The HC, Newton PN, Dance DAB, Campbell JI, Thwaites GE, Parry CM, Thanh DP Baker S (2018) Azithromycin resistance in *Shigella* spp. in Southeast Asia. *Antimicrobial Agents & Chemo* pii: AAC.01748-17. doi:

Abstract. Infection by *Shigella* spp. is a common cause of dysentery in Southeast Asia. Antimicrobials are thought to be beneficial for treatment, however antimicrobial resistance in *Shigella* spp. is becoming widespread. We aimed to assess the frequency and mechanisms associated with decreased susceptibility to azithromycin in Southeast Asian *Shigella* isolates and use these data to assess appropriate susceptibility breakpoints. *Shigella* isolated in Vietnam and Laos were screened for susceptibility against azithromycin (15µg) by disc diffusion and minimum inhibitory concentration (MIC). Phenotypic resistance was confirmed by PCR amplification of macrolide

Mr Oday and Dr Nana, visiting from the USA, with some of the 2002 team !

resistance loci. We compared the genetic relationships and plasmid contents of azithromycin resistant *S. sonnei* using whole genome sequences. From 475 available *Shigella* spp. isolated in Vietnam and Laos between 1994 and 2012, 6/181 *S. flexneri* (3.3%, MIC≥16g/L) and 16/294 *S. sonnei* (5.4%, MIC≥32g/L) were phenotypically resistant to azithromycin. PCR amplification confirmed a resistance mechanism in 22/475 (4.6%) isolates (19 mphA and 3 ermB). Susceptibility data demonstrated the acceptability of *S. flexneri* (MIC≥16g/L, zone≤15mm) and *S. sonnei* (MIC≥32g/L, zone≤11mm) breakpoints with <3% discrepancy. Phylogenetic analysis demonstrated that decreased susceptibility has arisen sporadically in Vietnamese *S. sonnei* on at least seven occasions between 2000 and 2009, but failed to become established. While the proposed susceptibility breakpoints may allow better recognition of resistant isolates, additional studies are required to assess the impact on clinical outcome. The potential emergence of azithromycin resistance highlights the need for alternative management options for *Shigella* infections in endemic countries.

19. Day N, Newton PN (2016) Scrub typhus and other tropical rickettsioses. IN: Infectious Diseases. Eds: Cohen J and Powderly WG. Mosby. Fourth Ed. [A textbook chapter on scrub typhus and rickettsial pathogens]

20. Dittrich S, Boudthasavong L, Keokhamhoung D, Phuklia W, Craig S, Tulsiani S, Burns M-A, Weier S, Dance D, Davone V, Vongsouvath M, Mayxay M, Phetsouvanh R, Newton PN, Woods K (in press) A prospective hospital study to evaluate the diagnostic accuracy of rapid diagnostic tests for the early detection of leptospirosis in Laos. *Am J Trop Med Hyg*.

Abstract. Leptospirosis is a globally important cause of acute febrile illness, and a common cause of non-malarial fever in Asia, Africa and Latin America. Simple rapid diagnostic tests (RDTs) are needed to enable health care workers, particularly in low resource settings, to diagnose leptospirosis early and give timely targeted treatment. This study compared four commercially available RDTs to detect human IgM against *Leptospira* spp. in a head-to-head prospective evaluation in Mahosot Hospital, Lao PDR. Patients with an acute febrile illness consistent with leptospirosis (n=695) were included in the study during the 2014 rainy season. Samples were tested with 4 RDTs: ('Test-it' (Life Assay, South Africa; n=418); 'Leptorapide' (Linnodee, Northern Ireland; n=492); 'Dual Path Platform' (DPP) (Chembio, USA; n=530); and 'SD-IgM' (Standard Diagnostics, South Korea; n=481)). Diagnostic performance characteristics were calculated and compared to a composite reference standard combining PCR (rrs), microscopic agglutination tests (MAT) and culture. Of all patients investigated, 39/695 (5.6%) were positive by culture, PCR or MAT. The sensitivity and specificity of the RDTs ranged greatly from 17.9-63.6% and 62.1-96.8%, respectively. None of the investigated RDTs reached a sensitivity or specificity of >90% for detecting *Leptospira* infections on admission. In conclusion, our investigation highlights the challenges associated with *Leptospira* diagnostics, particularly in populations with multiple exposures. These findings emphasize the need for extensive prospective evaluations in multiple endemic settings to establish the value of rapid tools for diagnosing fevers to allow targeted antibiotics.

21. Douangngeun B, Theppangna W, Phommachanh P, Chomdara K, Phiphakhavong S, Khounsy S, Mukaka M, Dance DAB, Blacksell SD (2017) Rabies surveillance in dogs in Lao PDR from 2010-2016. *PLoS Negl Trop Dis.* 11(6):e0005609. doi: 10.1371/journal.pntd.0005609.

Pierre Brossmann, Tara Black, Aluna Brossmann, Jennifer Boss and Sujittra Sukhapiwatana (Jiab, from MORU-Bangkok) about to go zip lining in Vang Vieng

Abstract. BACKGROUND: Rabies is a fatal viral disease that continues to threaten both human and animal health in endemic countries. The Lao People's Democratic Republic (Lao PDR) is a rabies-endemic country in which dogs are the main reservoir and continue to present health risks for both human and animals throughout the country. METHODS: Passive, laboratory-based rabies surveillance was performed for suspected cases of dog rabies in Vientiane Capital during 2010-2016 and eight additional provinces between 2015-2016 using the Direct Fluorescent Antibody Test (DFAT). RESULTS: There were 284 rabies positive cases from 415 dog samples submitted for diagnosis. 257 cases were from Vientiane Capital (2010-2016) and the remaining 27 cases were submitted during 2015-2016 from Champassak (16 cases), Vientiane Province (4 cases), Xieng Kuang (3 cases), Luang Prabang (2 cases), Saravan (1 case), Saisomboun (1 case) and Bokeo (1 case). There was a significant increase in rabies cases during the dry season (p = 0.004) (November to April; i.e., <100mm of rainfall per month). No significant differences were noted between age, sex, locality of rabies cases. CONCLUSION: The use of laboratory-based rabies surveillance is a useful method of monitoring rabies in Lao PDR and should be expanded to other provincial centers, particularly where there are active rabies control programs.

22. Hantrakun V, Thaipadungpanit J, Rongkard P, Srilohasin P, Amornchai P, Langla S, Mukaka M, Chantratita N, Wuthiekanun V, Dance DAB, Day NPJ, Peacock SJ, Limmathurotsakul D (2018) Presence of *B. thailandensis* and *B. thailandensis* expressing *B. pseudomallei*-like capsular polysaccharide in Thailand, and their associations with serological response to *B. pseudomallei*. *PLoS Negl Trop Dis*. 12(1):e0006193.

Abstract. BACKGROUND. *Burkholderia pseudomallei* is an environmental Gram-negative bacillus and the cause of melioidosis. *B. thailandensis*, some strains of which express a *B. pseudomallei*-like capsular polysaccharide (BTCV), is also commonly found in the environment in Southeast Asia but is considered non-pathogenic. The aim of the study was to determine the distribution of *B. thailandensis* and its capsular variant in Thailand and investigate whether its presence is associated with a serological response to *B. pseudomallei*. METHODOLOGY/PRINCIPAL FINDINGS: We evaluated the presence of *B. pseudomallei* and *B. thailandensis* in 61 rice fields in Northeast (n = 21), East (n = 19) and Central (n = 21) Thailand. We found BTCV in rice fields in East and Central but not Northeast Thailand. Fourteen fields were culture positive for *B. pseudomallei* alone, 8 for *B. thailandensis* alone, 11 for both *B. pseudomallei* and *B. thailandensis*, 6 for both B. thailandensis and BTCV, and 5 for *B. pseudomallei, B. thailandensis* and BTCV. Serological testing using the indirect hemagglutination assay (IHA) of 96 farmers who worked in the study fields demonstrated that farmers who worked in *B. pseudomallei*-positive fields had higher IHA titers than those who worked in *B. pseudomallei*-negative fields (median 1:40 [range: <1:10-1:640] vs. <1:10 [range: <1:10-1:320], p = 0.002). In a multivariable ordered logistic regression model, IHA titers were significantly associated with the presence of *B. pseudomallei* (aOR = 3.7; 95% CI 1.8-7.8, p = 0.001) but were not associated with presence of *B. thailandensis* (p = 0.32) or BTCV (p = 0.32). One sequence type (696) was identified for the 27 BTCV isolates tested. CONCLUSIONS/ SIGNIFICANCE: This is the first report of BTCV in Thailand. The presence of *B. pseudomallei* and *B. thailandensis* in the same field was not uncommon. Our findings suggest that IHA positivity of healthy rice farmers in Thailand is associated with the presence of *B. pseudomallei* in rice fields rather than *B. thailandensis* or BTCV.

23. Imwong M, Suwannasin K, Kunasol C, Sutawong K, Mayxay M, Rekol H, Smithuis FM, Hlaing TM, Tun KM, van der Pluijm RW, Tripura R, Miotto O, Menard D, Dhorda M, Day NPJ, White NJ, Dondorp AM (2017) The spread of artemisinin-resistant *Plasmodium falciparum* in the Greater Mekong

subregion: a molecular epidemiology observational study. *Lancet Infect Dis.* 17(5):491-497. doi: 10.1016/S1473-3099(17)30048-8.

Abstract. BACKGROUND: Evidence suggests that the PfKelch13 mutations that confer artemisinin resistance in falciparum malaria have multiple independent origins across the Greater Mekong subregion, which has motivated a regional malaria elimination agenda. We aimed to use molecular genotyping to assess antimalarial drug resistance selection and spread in the Greater Mekong subregion. METHODS: In this observational study, we tested Plasmodium falciparum isolates from Myanmar, northeastern Thailand, southern Laos, and western Cambodia for PfKelch13 mutations and for Pfplasmepsin2 gene amplification (indicating piperaquine resistance). We collected blood spots from patients with microscopy or rapid test confirmed uncomplicated falciparum malaria. We used microsatellite genotyping to assess genetic relatedness. FINDINGS: As part of studies on the epidemiology of artemisinin-resistant malaria between Jan 1, 2008, and Dec 31, 2015, we collected 434 isolates. In 2014-15, a single long PfKelch13 C580Y haplotype (-50 to +31·5 kb) lineage, which emerged in western Cambodia in 2008, was detected in 65 of 88 isolates from northeastern Thailand, 86 of 111 isolates from southern Laos, and 14 of 14 isolates from western Cambodia, signifying a hard transnational selective sweep. Pfplasmepsin2 amplification occurred only within this lineage, and by 2015 these closely related parasites were found in ten of the 14 isolates from Cambodia and 15 of 15 isolates from northeastern Thailand. C580Y mutated parasites from Myanmar had a different genetic origin. INTERPRETATION: Our results suggest that the dominant artemisinin-resistant P falciparum C580Y lineage probably arose in western Cambodia and then spread to Thailand and Laos, outcompeting other parasites and acquiring piperaquine resistance. The emergence and spread of fit artemisinin-resistant P falciparum parasite lineages, which then acquire partner drug resistance across the Greater Mekong subregion, threatens regional malaria control and elimination goals. Elimination of falciparum malaria from this region should be accelerated while available antimalarial drugs still remain effective.

24. Manivanh L, Pierret A, Rattanavong S, Kounnavongsa O, Buisson Y, Elliott I, Maeght J-, Xayyathip K, Silisouk J, Vongsouvath M, Phetsouvanh R, Newton PN, Lacombe G, Ribolzi O, Rochelle-Newall E, Dance DAB (2017) *Burkholderia pseudomallei* in a lowland rice paddy: seasonal changes and influence of soil depth and physico-chemical properties. *Sci Rep.* 7(1):3031.

Abstract. Melioidosis, a severe infection with the environmental bacterium *Burkholderia pseudomallei*, is being recognised increasingly frequently. What determines its uneven distribution within endemic areas is poorly understood. We cultured soil from a rice field in Laos for *B. pseudomallei* at different depths on 4 occasions over a 13-month period. We also measured physical and chemical parameters in order to identify associated characteristics. Overall, 195 of 653 samples (29.7%) yielded *B. pseudomallei*. A higher prevalence of *B. pseudomallei* was found at soil depths greater than the 30 cm currently recommended for *B. pseudomallei* environmental sampling. *B. pseudomallei* was associated with a high soil water content and low total nitrogen, carbon and organic matter content. Our results suggested that a sampling grid of 25 five metre square quadrats (i.e. 25 × 25 m) should be sufficient to detect *B. pseudomallei* at a given location if samples are taken at a soil depth of at least 60 cm. However, culture of *B. pseudomallei* in environmental samples is difficult and liable to variation. Future studies should both rely on molecular approaches and address the micro-heterogeneity of soil when investigating physico-chemical associations with the presence of *B. pseudomallei*.

25. Ming DKY, Rattanavong S, Bharucha T, Sengvilaipaseuth O, Dubot-Pérès A, Newton PN, Robinson MT (2017) *Angiostrongylus cantonensis* DNA in Cerebrospinal Fluid of Persons with Eosinophilic Meningitis, Laos. *Emerg Infect Dis.* 23(12):2112-2113.

Abstract. Definitive identification of *Angiostrongylus cantonensis* parasites from clinical specimens is difficult. As a result, regional epidemiology and burden are poorly characterized. To ascertain presence of this parasite in patients in Laos with eosinophilic meningitis, we performed quantitative PCRs on 36 cerebrospinal fluid samples; 4 positive samples confirmed the parasite's presence.

26. Newton PN (in press) Medicine Quality, Physicians and Patients. Oxford Textbook of Medicine

[A review of medicine quality and public health]

27. Nguyen VH, Dubot-Pérès A, Russell FM, Dance DAB, Vilivong K, Phommachan S, Syladeth C, Lai J, Lim R, Morpeth M, Mayxay M, Newton PN, Richet H, de Lamballerie X (2017) Acute respiratory infections in hospitalized children in Vientiane, Lao PDR - the importance of Respiratory Syncytial Virus. *Sci Rep.* 7(1):9318.

Abstract. The Human respiratory syncytial virus (RSV) is one of the most important viral pathogens, causing epidemics of acute respiratory infection (ARI), especially bronchiolitis and pneumonia, in children worldwide. To investigate the RSV burden in Laos, we conducted a one-year study in children <5 years old admitted to Mahosot Hospital, Vientiane Capital, to describe clinical and epidemiological characteristics and predictive factors for severity of RSV-associated ARI. Pooled nasal and throat swabs were tested using multiplex real-time PCR for 33 respiratory pathogens (FTD® kit). A total of 383 patients were included, 277 (72.3%) of whom presented with pneumonia. 377 (98.4%) patients were positive for at least one microorganism, of which RSV was the most common virus (41.0%), with a peak observed between June and September, corresponding to the rainy season. Most RSV inpatients had pneumonia (84.1%), of whom 35% had severe pneumonia. Children <3-months old were a high-risk group for severe pneumonia, independently of RSV infection. Our study suggests that RSV infection is frequent in Laos and commonly associated with pneumonia in hospitalized young children. Further investigations are required to provide a better overall view of the Lao nationwide epidemiology and public health burden of RSV infection over time.

28. Ombelet S, Ronat J-B, Walsh T, Yansouni CP, Cox J, Vlieghe E, Martiny D, Semret M, Vandenberg O, Jacobs J. On behalf of the BACTI-LRS working group (including David Dance & Paul Newton) (*in press*). Clinical bacteriology in low resource settings – not tomorrow's but today's solutions. *Lancet Infectious Diseases*

Abstract. Low-resource settings (LRS) are disproportionately burdened by infectious diseases and antimicrobial resistance (AMR). Good quality bacteriology is a prerequisite for effective AMR control, but LRS face infrastructural, technical and behavioural challenges when implementing clinical bacteriology. This article explores the needs for successful implementation of clinical bacteriology in LRS. The majority of microbiological techniques and equipment have not been developed for the specific needs of LRS. Pending the arrival of a new generation of LRS-friendly diagnostics, we have focused on improving, adapting and implementing conventional, culture-based techniques. LRS priorities include harmonized, quality-assured and "tropicalized" equipment, consumables and techniques as well as rationalized bacterial identification and AMR testing. Diagnostics should be integrated into clinical care and patient management; moreover, clinically relevant specimens must be appropriately selected and prioritized. Open-access training materials and information management tools should be developed. We also advocate on-site validation and field-adoption of diagnostics in LRS, with considerable shortening of the time between development and implementation of diagnostics. We argue that implementing clinical bacteriology in LRS improves patient management, provides valuable surveillance for local antibiotic treatment guidelines and national policies, and augments AMR containment and hospital infection prevention and control.

29. Peyraud N, Rafael F, Parker LA, Quere M, Alcoba G, Korff C, Deats M, Bourdillon Esteve P, Cabrol J-C, Serafini M, Ciglenecki I, Rull M, Amine Larabi I, Baud F, Grandesso F, Ilunga B K, Alvarez J-C, Newton PN (2017) A large epidemic of dystonic reactions in central Africa: the possible role of falsified diazepam containing haloperidol. *Lancet Global Health* 5, 3137-e138.

[In December 2014, patients with suspected meningitis were reported by the Ituri Health District, in the northeast Democratic Republic of Congo. In January 2015, Médecins sans Frontières (MSF) was approached by the Ministry of Health (MoH) to support outbreak investigation and response. At MoH and MSF case-management sites, patients' demographic characteristics, clinical features, and outcome were described. Cerebrospinal fluid was analysed for evidence of bacterial meningitis, and urine and 39 medicine samples underwent toxicological investigations. Initial investigations suggested that bacterial meningitis was not the aetiology. Patients presented with acute dystonic reactions affecting the muscles of the face, eyes, neck, tongue, and upper limbs with Parkinsonism and oculogyric crises. Over eight months, there were over one thousand hospitalisations. The urine from all

Tree resin - kii kang - for fixing blades into handles, Luang Nam Tha Market

patient samples (n=9) tested positive for haloperidol. One tablet type sold as 'diazepam' in the community unexpectedly contained haloperidol as the sole active pharmaceutical ingredient, suggesting that this large outbreak was due to haloperidol toxicity from falsified diazepam. How diazepam came to contain haloperidol is under investigation by national/international authorities. This outbreak emphasizes the need for thorough investigation of atypical presentations of common diseases and for considering toxicity from falsified medicines. Increased funding pressure and scarce resources are likely to risk disadvantaged populations accessing unreliable sources of medicine. Strengthening the capacity of medicine regulatory authorities is a key requirement to ensure the quality of medicines, especially for vulnerable populations.]

30. Phetsouvanh R, Habe S, Newton P, Vongsouvaht M, Horii H, Doanh PN , Nawa Y (2018) Spontaneous Emergence Of A *Gnathostoma spinigerum* Adult Worm From The Abdominal Skin Of A Laotian Woman: A Case Report. Southeast Asian J Trop Med Public Health 49 (1) 1-5.

Abstract. Gnathostomiasis caused by infection with the Spirurine nematode, *Gnathostoma* species, is a common fish-borne parasitic zoonosis in Asia. We present here the case of the spontaneous emergence of an adult *Gnathostoma spinigerum* worm from the abdominal skin of a Laotian woman. We review the literature on gnathostomiasis and discover that infective *G. spinigerum* larvae can grow into immature and mature worms in humans more commonly than expected.

31. Phuong TLT, Rattanavong S, Vongsouvath M, Davong V, Lan NPH, Campbell JI, Thwaites GE, Newton PN, Dance D, Baker S (2018) Non-typhoidal *Salmonella* serovars associated with invasive and non-invasive disease in Lao People's Democratic Republic. *Trans Royal Soc Trop Med Hyg*. 2018 Jan 12. doi: 10.1093/trstmh/trx076.

Abstract. Invasive non-typhoidal *Salmonella* (iNTS) infections are a well-described cause of mortality in children and HIV-infected adults in sub-Saharan Africa; there is additionally an ill-defined burden of iNTS disease in Southeast Asia. Aiming to investigate the causative serovars of non-invasive and iNTS disease and their associated antimicrobial susceptibility profiles in Lao PDR, we performed MLST and antimicrobial susceptibility profiling on 168 NTS (63 blood and 105 faecal) organisms isolated in Lao between 2000 and 2012. Six different serovars were isolated from blood. *S.* Enteritidis (n=28), *S.* Typhimurium (n=19), and *S.* Choleraesuis (n=11) accounted for >90% (58/63) of the iNTS cases. In contrast, the isolates from diarrhoeal faeces were comprised of 18 different serovars, the mostly commonly identified being *S.* Typhimurium (n=28), *S.* Weltevreden (n=14), and *S.* Stanley (n=15). *S.* Enteritidis and *S.* Choleraesuis were significantly more associated with systemic disease than diarrhoeal disease in this patient group (p<0.001). Organisms isolated from faecal samples were significantly less likely to be susceptible to ampicillin and trimethoprim-sulphamethoxazole than those isolated from blood (p<0.05). The majority (65%; 41/63) of the bloodstream isolates were non-susceptible to ciprofloxacin; this proportion was significantly greater than in the organisms isolated from faeces (p<0.001; Fisher's exact test). We find a differing distribution of *Salmonella* STs/serovars between those with iNTS and non-invasive disease in Lao. However, the distribution of iNTS serovars and ST is comparable to other locations in Southeast Asia. We conclude that there is a small but not-insignificant burden of iNTS disease in Lao; further clinical and epidemiological investigations are required to assess mortality and the role of co-morbidities such as HIV.

32. Phouangsouvanh S, Mayxay M, Keoluangkhot V, Vongsouvath M, Davong V, Dance DAB (2017) Antibiotic susceptibility of *Neisseria gonorrhoeae* in Vientiane, Lao PDR. *J Glob Antimicrob Resist.* 2017 Dec 8. pii: S2213-7165(17)30231-X.

Abstract. OBJECTIVES: To determine the antibiotic susceptibility of *N. gonorrhoeae* in the Lao People's Democratic Republic (Laos). METHODS: We obtained 158 gonococcal isolates from 12,281 genital samples routinely submitted to a diagnostic laboratory in Vientiane, Laos between 2011 and 2015 and determined their susceptibility to five antibiotics by a standard disk diffusion method. RESULTS: The rates of resistance to penicillin (by beta-lactamase production), tetracycline and ciprofloxacin were 89.9%, 99.3% and 84.8% respectively. All isolates were sensitive to ceftriaxone and spectinomycin. CONCLUSIONS: This situation is similar to that in neighboring countries, but fortunately means that the latest Lao national guidelines for treating gonorrhoea should still be effective.

Tak Bhat for Ok Phan Sa at Wat Sisaket, October 2017

33. Robinson MT, Jatupornpimol N, Sachaphimukh S, Lönnkvist M, Ruecker A, Cheah PY (2017) The First Pint of Science Festival in Asia. *Science Communication.* 39(6) 810– 820.

Abstract. The Pint of Science Festival is the largest annual international science festival. So far the event has been held simultaneously in Europe, North America, South America, Africa, and Australia but not in Asia. Pint of Science Thailand was held for the first time this year, in Thailand's capital, Bangkok. This article briefly discusses some of the successes, challenges, and lessons learnt associated with running

the first Pint of Science event in Asia, a culture very different to the Western Hemisphere cities that have currently hosted Pint of Science events.

34. Sengvilaipaseuth O, Phommasone K, de Lamballerie X, Vongsouvath M, Phonemixay O, Blacksell SD, Mayxay M, Keomany S, Souvannasing P, Newton PN, Dubot-Pérès A (2017) Temperature stability of a Dengue Rapid Diagnostic Test under tropical climatic conditions: A follow up study. *PloS One*. 12(1):e0170359.

Abstract. The Dengue Duo Rapid Diagnostic Test (SD Dengue RDT) has good specificity and sensitivity for dengue diagnosis in rural tropical areas. In a previous study, using four control sera, we demonstrated that that the diagnostic accuracy of these RDTs remains stable after long-term storage at high temperatures. We extended this study by testing sera from 119 febrile patients collected between July-November 2012 at Salavan Provincial Hospital (southern Laos) with RDTs stored for 6 months at 4°C, 35° and in a hut (miniature traditional house) at Lao ambient temperatures. The dengue NS1 antigen results from RDTs stored at 35° C and in the hut demonstrated 100% agreement with those stored at 4°C. However, lower positive percent agreements, with broad 95%CI, were observed for the tests: IgM, 60% (14.7-94.7) and 40% (5.3-85.3) for RDTs store at 35°C and in the hut, compared to those stored at 4°C, respectively. This study strengthens the evidence of the robustness of the NS1 antigen detection RDT for the diagnosis of dengue after storage at tropical temperatures.

35. Sengvilaipaseuth O, Castonguay-Vanier J, Chanthongthip A, Phonemixay O, Thongpaseuth S, Vongsouvath M, Newton PN, Bharucha T, Dubot-Pérès A (in press) Poor Performance of two Rapid Immunochromatographic Assays for anti-JEV IgM Detection in Serum and Cerebrospinal Fluid from Patients with Suspected Japanese Encephalitis Virus Infection in Laos. *Trans Royal Soc Trop Med & Hyg*.

Abstract. Background: Japanese encephalitis virus (JEV) is a leading identified cause of encephalitis in Asia, often occurring in rural areas with poor access to laboratory diagnostics. We evaluated two rapid diagnostic tests (RDTs) for anti-JEV immunoglobulin M (IgM) detection. Methods: Consecutive cerebrospinal fluid and serum from 388 patients (704 samples) with suspected JEV infections admitted to six hospitals in Laos were tested with one of two SD-Bioline anti-JEV IgM RDTs and the World Health Organization standard anti-JEV IgM enzyme-linked immunosorbent assay (ELISA; Panbio Japanese Encephalitis-Dengue IgM Combo ELISA. Results and Conclusions: The performance of both RDTs showed strikingly low sensitivity in comparison to anti-JEV IgM antibody capture ELISA (2.1-51.4%), suggesting low sensitivity of the RDTs. We highlight the fundamental prerequisite to validate RDTs prior to use to ensure that they meet standards for testing

36. Suttisunhakul V, Pumpuang A, Ekchariyawat P, Wuthiekanun V, Elrod MG, Turner P, Currie BJ, Phetsouvanh R, Dance DA, Limmathurotsakul D, Peacock SJ, Chantratita N (2017) Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry for the identification of *Burkholderia pseudomallei* from Asia and Australia and differentiation between *Burkholderia* species. *PLoS One*. 12(4):e0175294. doi: 10.1371/journal.pone.0175294.

Abstract. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) is increasingly used for rapid bacterial identification. Studies of *Burkholderia pseudomallei* identification have involved small isolate numbers drawn from a restricted geographic region. There is a need to expand the reference database and evaluate *B. pseudomallei* from a wider geographic distribution that more fully captures the extensive genetic diversity of this species. Here, we describe the evaluation of over 650 isolates. Main spectral profiles (MSP) for 26 isolates of *B. pseudomallei* (N = 5) and other *Burkholderia* species (N = 21) were added to the Biotyper database. MALDI-TOF MS was then performed on 581 *B. pseudomallei*, 19 *B. mallei*, 6 *B. thailandensis* and 23 isolates representing a range of other bacterial species. *B. pseudomallei* originated from northeast and east Thailand (N = 524), Laos (N = 12), Cambodia (N = 14), Hong Kong (N = 4) and Australia (N = 27). All 581 *B. pseudomallei* were correctly identified, with 100% sensitivity and specificity. Accurate identification required a minimum inoculum of 5 x 107 CFU/ml, and identification could be performed on spiked blood cultures after 24 hours of incubation. Comparison between a dendrogram constructed from MALDI-TOF MS main spectrum profiles and a phylogenetic tree based on recA gene sequencing demonstrated that MALDI-TOF MS distinguished between *B. pseudomallei* and *B. mallei*, while the recA tree did not. MALDI-TOF MS is an accurate method for the

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identification of *B. pseudomallei*, and discriminates between this and other related *Burkholderia* species.

37. Stergachis A, Batson J, Crawford S, Fernandez FM, Kaale EA, Kalyanaraman R, Kwiringira W, Newton PN, Olsen B, Rodriguez J, Wilson B, Young SJ, Zook A, Roth LM (2017) Evaluation of Screening Technologies for Assessing Medicine Quality. *Pharmacopeial Forum.* http://www.usppf.com/pf/pub/index.htm

Abstract. Various portable screening technologies have been developed to assess the quality and authenticity of medicines and thereby combat the growing global problem of substandard and falsified (SF) medicines. However, the capabilities and limitations of many technologies are not well characterized, particularly when used outside the laboratory, for example in supply chain testing or at the point of care. This Stimuli article addresses the need for structured, effective approaches to performing a pragmatic review of a given technology. The information collected during the review can inform the selection and deployment of the technology of interest, which in turn can help prevent SF drugs from reaching vulnerable populations. Comments from the public and stakeholders are requested as this review will subsequently become a USP informational chapter.

38. Teerawattanasook N, Tauran PM, Teparrukkul P, Wuthiekanun V, Dance DAB, Arif M, Limmathurotsakul D (2017) Capacity and Utilization of Blood Culture in Two Referral Hospitals in Indonesia and Thailand. *Am J Trop Med Hyg.* 97(4):1257-1261. doi: 10.4269/ajtmh.17-0193.

Abstract. It is generally recommended that sepsis patients should have at least two blood cultures obtained before antimicrobial therapy. From 1995 to 2015, the number of blood cultures taken each year in a 1,100-bed public referral hospital in Ubon Ratchathani northeast Thailand rose from 5,235 to 56,719, whereas the number received in an 840-bed referral public hospital in South Sulawesi, Indonesia, in 2015 was 2,779. The proportion of patients sampled for blood cultures out of all inpatients in

South Sulawesi in 2015 (9%; 2,779/30,593) was lower than that in Ubon Ratchathani in 2003 (13%; 8,707/66,515), at a time when health expenditure per capita in the two countries was comparable. Under-use of bacterial cultures may lead to an underestimate and underreporting of the incidence of antimicrobial-resistant infections. Raising capacity and utilization of clinical microbiology laboratories in developing countries, at least at sentinel hospitals, to monitor the antimicrobial resistance situation should be prioritized.

39. Tun STT, von Seidlein L, Pongvongsa T, Mayxay M, Saralamba S, Kyaw SS, Chanthavilay P, Celhay O, Nguyen TD, Tran TN, Parker DM, Boni MF, Dondorp AM, White LJ (2017) Towards malaria elimination in Savannakhet, Lao PDR: mathematical modelling driven strategy design. *Malar J.* 16(1):483. doi: 10.1186/s12936-017-2130-3.

Abstract. BACKGROUND: The number of *Plasmodium falciparum* malaria cases around the world has decreased substantially over the last 15 years, but with the spread of resistance against anti-malarial drugs and insecticides, this decline may not continue. There is an urgent need to consider alternative, accelerated strategies to eliminate malaria in countries like Lao PDR, where there are a few remaining endemic areas. A deterministic compartmental modelling tool was used to develop an integrated strategy for *P. falciparum* elimination in the Savannakhet province of Lao PDR. The model was designed to include key aspects of malaria transmission and integrated control measures, along with a user-friendly interface. RESULTS: Universal coverage was the foundation of the integrated strategy, which took the form of the deployment of community health workers who provided universal access to early diagnosis, treatment and long-lasting insecticidal nets. Acceleration was included as the deployment of three monthly rounds of mass drug administration targeted towards high prevalence villages, with the addition of three monthly doses of the RTS,S vaccine delivered en masse to the same high prevalence sub-population. A booster dose of vaccine was added 1 year later. The surveillance-as-intervention component of the package involved the screening and treatment of individuals entering the simulated population. CONCLUSIONS: In this modelling approach, the sequential introduction of a series of five available interventions in an integrated strategy was predicted to be sufficient to stop malaria transmission within a 3-year period. These interventions comprised universal access to early diagnosis and adequate treatment, improved access to long-lasting insecticidal nets, three monthly rounds of mass drug administration together with RTS,S vaccination followed by a booster dose of vaccine, and screening and treatment of imported cases.

40. Wiersinga W, Virk H, Limmathurotsakul D, Dance D, Peacock S, Torres A, Currie B (2018) Melioidosis. *Nature Reviews Disease Primers*. 4:17107.

Abstract. *Burkholderia pseudomallei* is a Gram-negative environmental bacterium and the aetiological agent of melioidosis, a life-threatening infection that is estimated to account for ~89,000 deaths per year worldwide. Diabetes mellitus is a major risk factor for melioidosis, and the global diabetes pandemic could increase the number of fatalities caused by melioidosis. Melioidosis is endemic across tropical areas, especially in Southeast Asia and northern Australia. Disease manifestations can range from acute septicaemia to chronic infection, as the facultative intracellular lifestyle and virulence factors of *B. pseudomallei* promote survival and persistence of the pathogen within a broad range of cells, and the bacteria can manipulate the host's immune responses and signalling pathways to escape surveillance. The majority of patients present with sepsis, but specific clinical presentations and their severity vary depending on the route of bacterial entry (skin penetration, inhalation or ingestion), host immune function and bacterial strain and load. Diagnosis is based on clinical and epidemiological features as well as bacterial culture. Treatment requires long-term intravenous and oral antibiotic courses. Delays in treatment due to difficulties in clinical recognition and laboratory diagnosis often lead to poor outcomes and mortality can exceed 40% in some regions. Research into *B. pseudomallei* is increasing, owing to the biothreat potential of this pathogen and increasing awareness of the disease and its burden; however, better diagnostic tests are needed to improve early confirmation of diagnosis, which would enable better therapeutic efficacy and survival.

41. Woods K, Nic-Fhogartaigh C, Arnold C, Boutthasavong L, Phuklia W, Lim C, Chanthongthip A, Tulsiani SM, Craig S,Burns MA, Weier SL, Davong V, Sihalath S, Limmathurotsakul D, Dance DAB, Shetty N, Zambon M, Newton PN, Dittrich S (2017) A comparison of two molecular methods for diagnosing leptospirosis from three different sample

The Chiggers and Australian Embassy Football Teams - The Chiggers Won !

types in patients presenting with fever in Laos. *Clin Microbiol Infect*. 2017 Oct 26.

Abstract. OBJECTIVES: To compare two molecular assays (rrs quantitative PCR (qPCR) versus a combined 16SrRNA and LipL32 qPCR) on different sample types for diagnosing leptospirosis in febrile patients presenting to Mahosot Hospital, Vientiane, Laos. METHODS: Serum, buffy coat and urine samples were collected on admission, and follow-up serum ~10 days later. *Leptospira* spp. culture and microscopic agglutination tests (MAT) were performed as reference standards. Bayesian latent class modelling was performed to estimate sensitivity and specificity of each diagnostic test. RESULTS: In all, 787 patients were included in the analysis: 4/787 (0.5%) were *Leptospira* culture positive, 30/787 (3.8%) were MAT positive, 76/787 (9.7%) were rrs qPCR positive and 20/787 (2.5%) were 16SrRNA/LipL32 qPCR positive for pathogenic *Leptospira* spp. in at least one sample. Estimated sensitivity and specificity (with 95% CI) of 16SrRNA/LipL32 qPCR on serum (53.9% (33.3%-81.8%); 99.6% (99.2%-100%)), buffy coat (58.8% (34.4%-90.9%); 99.9% (99.6%-100%)) and urine samples (45.0% (27.0%-66.7%); 99.6% (99.3%-100%)) were comparable with those of rrs qPCR, except specificity of 16SrRNA/LipL32 qPCR on urine samples was significantly higher (99.6% (99.3%-100%) vs. 92.5% (92.3%-92.8%), p <0.001). Sensitivities of MAT (16% (95% CI 6.3%-29.4%)) and culture (25% (95% CI 13.3%-44.4%)) were low. Mean positive Cq values showed that buffy coat samples were more frequently inhibitory to qPCR than either serum or urine (p <0.001). CONCLUSIONS: Serum and urine are better samples for qPCR than buffy coat, and 16SrRNA/LipL32 qPCR performs better than rrs qPCR on urine. Quantitative PCR on admission is a reliable rapid diagnostic tool, performing better than MAT or culture, with significant implications for clinical and epidemiological investigations of this global neglected disease.

42. Yeap AD, Woods K, Dance DAB, Pichon B, Rattanavong S, Davong V, Phetsouvanh R, Newton PN, Shetty N, Kearns AM (2017) Molecular Epidemiology of *Staphylococcus aureus* Skin and Soft Tissue Infections in the Lao People's Democratic Republic. *Am J Trop Med Hyg*. 2017 May 30. doi: 10.4269/ajtmh.16-0746.

Abstract. This is the first report of the molecular epidemiology of *Staphylococcus aureus* from skin and soft tissue infections (SSTI) in Laos. We selected a random sample of 96 *S. aureus* SSTI isolates received by the Microbiology Laboratory, Mahosot Hospital, Vientiane, between July 2012 and June 2014, including representation from seven referral hospitals. Isolates underwent susceptibility testing by Clinical and Laboratory Standards Institute methods, spa typing and DNA microarray analysis, with

whole genome sequencing for rare lineages. Median patient age was 19.5 years (interquartile range 2-48.5 years); 52% (50) were female. Forty-three spa types, representing 17 lineages, were identified. Fifty-eight percent (56) of all isolates encoded Panton-Valentine leukocidin (PVL), representing six lineages: half of these patients had abscesses and three had positive blood cultures. The dominant lineage was CC121 (39; 41%); all but one isolate encoded PVL and 49% (19) were from children under five. *Staphyococcus argenteus* was identified in six (6%) patients; mostly adults > 50 years and with diabetes. Six isolates (6%) belonged to rare lineage ST2885; two possibly indicate cross-infection in a neonatal unit. One isolate from a previously undescribed lineage, ST1541, was identified. Antibiotic resistance was uncommon except for penicillin (93; 97%) and tetracycline (48; 50%). Seven (7%) isolates were methicillin-resistant *S. aureus* (MRSA), belonging to ST239-MRSA-III, CC59-MRSA-V(T) Taiwan Clone, ST2250-MRSA-IV, ST2885-MRSA-V and CC398-MRSA-V. Globally widespread CC5 and CC30 were absent. There are parallels in *S. aureus* molecular epidemiology between Laos and neighboring countries and these data highlight the prominence of PVL and suggest infiltration of MRSA clones of epidemic potential from surrounding countries.

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43. Zellweger RM, Carrique-Mas J, Limmathurotsakul D, Day NPJ, Thwaites GE, Baker, Southeast Asia Antimicrobial Resistance Network = Ashley E, de Balogh K, Baird K, Basnyat B, Benigno C, Bodhidatta L, Chantratita N, Cooper B, Dance D, Dhorda M, van Doorn R, Dougan G, Hoa NT, Ip M, Lawley T, Lim C, Lin TK, Ling C, Lubell Y, Mather A, Marks F, Mohan VR, Newton P, Paris D, Thomson N, Turner P, Serichantalergs O, Smithuis F, Wuthiekanun V, White N, Li Yang H (2017) A current perspective on antimicrobial resistance in Southeast Asia. *J Antimicrob Chemother*. 72(11):2963-2972. doi: 10.1093/jac/dkx260.

Abstract. Southeast Asia, a vibrant region that has recently undergone unprecedented economic development, is regarded as a global hotspot for the emergence and spread of antimicrobial resistance (AMR). Understanding AMR in Southeast Asia is crucial for assessing how to control AMR on an international scale. Here we (i) describe the current AMR situation in Southeast Asia, (ii) explore the mechanisms that make Southeast Asia a focal region for the emergence of AMR, and (iii) propose ways in which Southeast Asia could contribute to a global solution.