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专论与综述

耐药微生物和抗生素耐药基因与全健康

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摘　要：因人类的各种活动，耐药微生物和抗生素耐药基因在“人-动物-环境”界面发生跨物种和跨生境的传播。将人类、动物和环境视作有机整体的“全健康” (One Health)理念有望成为解决这种传播的有效策略。抗生素及其代谢活性产物在环境中富集，再经动物及动物制品传播到人，产生耐药微生物并造成耐药基因的传播。本文综述了人-动物-环境界面耐药菌和抗生素耐药基因传播的流动与循环，总结了我国和其他国家应对抗生素耐药性问题的政策，倡导更多的国家和地区将“全健康”理念和方法用于控制抗生素耐药性传播；通过医疗卫生部门、食品药品监督管理部门、农林渔牧部门与教育、财政等多部门合作来应对抗生素耐药性的全球挑战。

关键词：微生物；微生物耐药性；耐药基因；全健康

Antibiotic-resistant microbes, antibiotic resistance genes and One Health

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Abstract: Antibiotic-resistant bacteria and antibiotic-resistance genes spread across species and habitats due to various human activities at the human-animal-environment interface. One Health that treats humans, animals and the environment as an organic whole is expected to become an effective

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strategy to mitigate such transmission. Due to human production activities, antibiotics and their metabolites are enriched in the environment, and then spread to people through animals or animal products, thus screening out resistant bacteria and causing the spread of resistance genes. This paper summarizes the main modes of transmission and the relationship between them and outlines Chinese and other countries' national plans to combat antibiotic resistance. We advocate that countries and regions use the concept and method of One Health to control the spread of antibiotic resistance. In addition, we should deal with the global challenge of antibiotic resistance through multisectoral collaboration among the medical and health sectors, food and drug administration, agriculture, forestry, fisheries, husbandry, education, and finance.

Keywords: microorganism; microbial resistance; antibiotic resistance genes; One Health

全健康(One Health)是一种在地方、区域和全球 3 个层面开展工作的跨学科和跨部门协作理念，核心目标在于探索人、动物和环境之间的复杂关系，通过医学、兽医学和环境科学等学科的交叉，以及经济、农业、地理和政策等领域的合作交流，实现个体健康、群体健康和生态健康。抗生素耐药性在人-动物-环境界面的流动与循环对人、动物、环境的健康都产生了极大威胁[1]，是适用于全健康理念和模式关注的问题之一。2015 年 5 月召开的世界卫生大会通过了《抗生素耐药性全球行动计划》(Global Action Plan on Antimicrobial Resistance)，该计划指出抗生素耐药性不仅对人类常规医疗活动产生重大威胁，也会对人类为应对传染病采取的有效公共卫生措施的可持续性产生负面影响[2-3]。不仅如此，在农业、畜牧业、水产养殖业施用抗生素也对生物产生严重危害[4]。微生物能够通过可移动基因元件(mobile genetic elements，MGE)的水平转移(horizontal gene transfer，HGT)获得抗生素耐药基因(antibiotic resistance genes，ARGs)，并进一步造成其在人-动物-环境中的流动传播[5-9]。抗生素耐药菌(antibiotic resistance bacteria，ARB)和耐药基因也被定义为新型环境污染物，对地表水、地下水和土壤产生负面影响，并进一步危害公众健康[10]。由于抗生素耐药菌和耐药基因会形成跨生境和跨物种的传播，因此，从全健康角度综合理解人、动物和环境微生物群之间的联系对于应对这一全球性公共健康挑战至关重要[11]。

本文从全健康视角综述了人、动物、环境中抗生素耐药微生物和抗生素耐药基因的流动和循环过程，并对以“全健康”理念应对抗生素耐药性进行了展望。

1 抗生素耐药性在人-动物-环境界面的传播

人类的生产生活、医疗活动及全球一体化的不断发展均会促进耐药性在人-动物-环境界面的全球传播[12]，其中包括了耐药基因和耐药微生物的传播，但耐药基因的传播更隐匿、更多样化，易造成耐药性更广泛的播散(图 1)。

1.1 人类活动造成不同界面间耐药性的传播

1.1.1 抗生素的生产

在抗生素的生产过程中，具有活性的中间产物和药物本身均可能在生产时排入制药废水而进入自然环境[13-14]，或在临床使用之前的运输、销售过程中因意外泄漏排入环境[15]，与其他共选择剂共同作用，促进耐药基因的转移和传播。

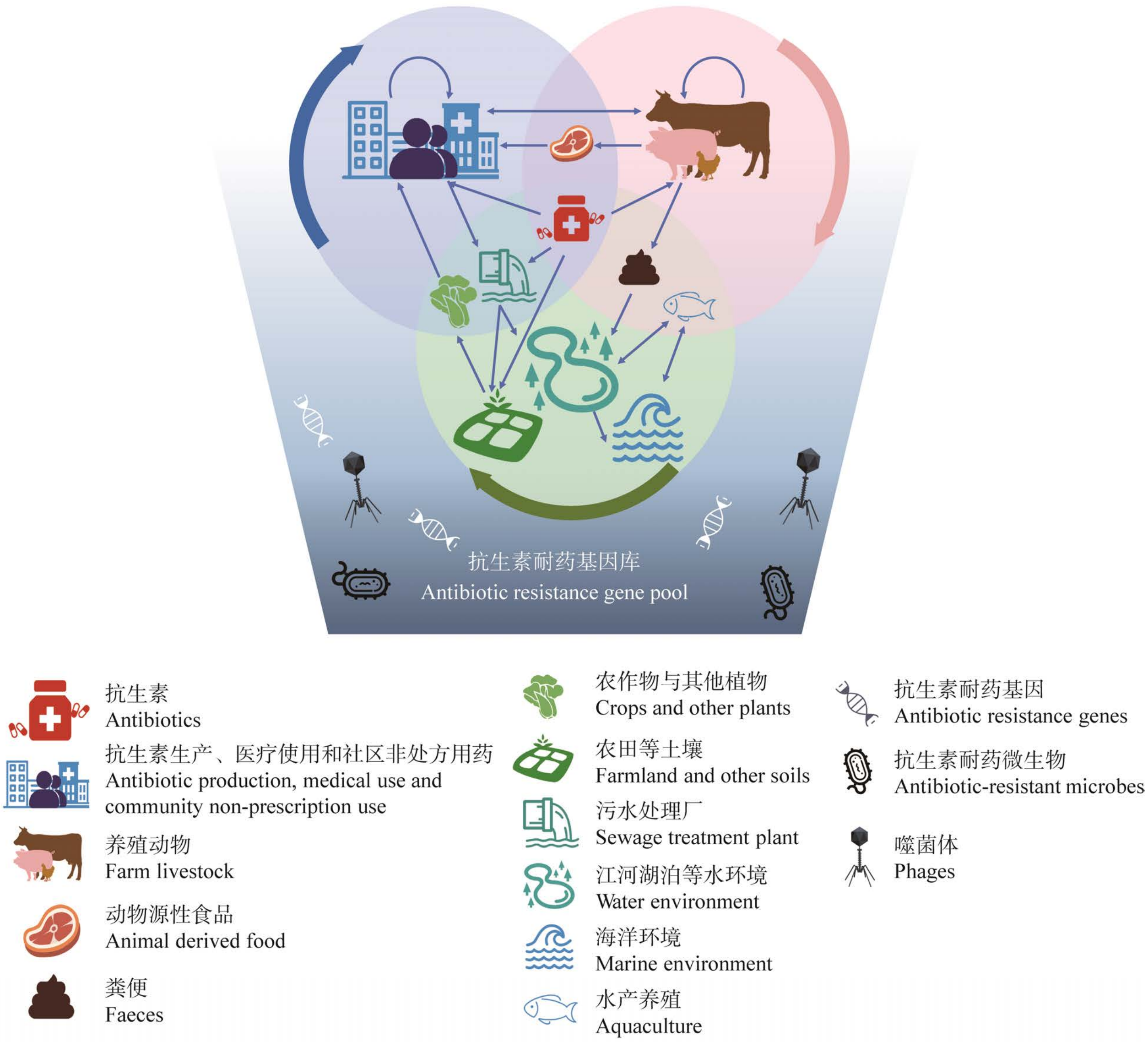

图 1　抗生素耐药基因在人-动物-环境界面的传播　微生物可以从抗生素耐药基因库中获得耐药基因。抗生素耐药基因可以通过直接或间接的方式在人、动物和环境之间流动、循环

Figure 1　Transmission of antibiotic resistance genes at the human-animal-environment interfaces. Antibiotic-resistant microbes often acquire resistance genes from the pool. Antibiotic resistance genes can flow and circulate among human, animals and the environment directly or indirectly.

1.1.2　抗生素的使用

医院内抗生素的使用是抗生素耐药性向环境中转移的主要原因[16]。医院排出的废水、废物和医院污泥中均含有高水平的耐药菌和耐药基因[17-18]。微生物暴露于常规城市废水并不会出现耐药性改变，而微生物暴露于医院废水则与磺胺类抗生素耐药性的比例增加有关[19]。

在中低收入国家，抗生素在社区、家庭中的误用和滥用是耐药性产生和传播的重要驱动因素[20]。居民服药后未经转化的抗生素及其代

谢产物与尿液、粪便一起排出，进入污水处理厂或自然环境中，从而促进耐药微生物和耐药基因在人和环境中的转移[21]。

1.1.3 微生态制剂的使用

近年来,随着对微生物组相关研究的深入，调控微生物组的微生态制剂被广泛应用于食品、药品、养殖畜牧业饲料添加等领域[22-23]。微生态制剂中含有活菌，其携带的耐药基因也存在摄入后引起播散的可能。Liu 等对分离自发酵乳制品和医药产品中的 41 株乳酸菌进行研究发现，大多数菌株对环丙沙星、阿米卡星、甲氧苄啶/磺胺甲恶唑和庆大霉素耐药，并发现携带耐药基因的商用菌株存在[24]。此外，在针对多株益生菌的安全性评价研究中，也发现耐药基因在菌株中的存在，成为其可能的安全风险之一[25-27]。

1.2 动物用抗生素造成不同界面间耐药性的传播

1.2.1 家禽牲畜与抗生素耐药性的传播

因具有抗病、促生长的作用，抗生素在畜牧业中广泛使用[23]。动物中持续使用抗生素会促进耐药微生物的出现并加强选择压力[20]。目前，欧洲已经完全禁止抗生素作为生长促进剂给予牲畜，美国也禁止在家禽养殖业中使用喹诺酮类抗生素，但全球范围内仍有很多国家以预防为目的添加抗生素喂饲牲畜[28]。

抗生素会通过牲畜的尿液和粪便从体内排出，通过土壤、地表径流、地下水等转移到环境中并传播[29-30]。粪便堆肥可成为耐药基因交换的场所及在土壤和水环境中转移的媒介，这使得人与家养牲畜和家禽粪便中的耐药菌组成也显著相关[31]。

携带耐药基因的微生物也可通过人与动物的直接接触传播，这一现象不仅发生在动物源性食品加工厂中[32]，还在居民与牲畜共用生活区的欠发达地区出现[33]。人类也可通过动物性食物的摄入接触耐药微生物[34]。

1.2.2 水产养殖与抗生素耐药性的传播

水产养殖业中抗生素的使用与城市污水的排放共同推动了水环境内抗生素耐药微生物的选择和传播[35-36]。仅在海水养殖场的表层水样中就可检出包括水产养殖业最常用的磺胺增效剂甲氧苄啶在内的 11 种抗生素[37]。综合养殖场水样中粘菌素抗性基因 *mcr* 和替加环素抗性基因 *tet(X)*的总丰度均高于单养淡水养殖场的水样[38]。

在水产养殖场中施用高剂量的抗生素还会对水产品产生毒性作用，并在水产动物肌肉中蓄积，人类可以通过食用水产品而间接摄入抗生素，从而导致肠道菌群获得耐药性[39]。

1.2.3 宠物、野生动物与抗生素耐药性的传播

宠物和野生动物也是耐药菌和耐药基因的储存库[40]。在宠物中使用抗生素也有助于耐药微生物从动物向人转移[41-42]。野生鸟类可以通过与人类接触获得多种耐药基因，而且其粪便中的浓度与偶尔喂食抗生素的家禽和牲畜相当[43]。此外，鹿、狐狸等哺乳动物也可作为耐药微生物的宿主和耐药基因传播的潜在媒介[44]。

1.3 环境中抗生素耐药性在不同界面的传播

1.3.1 土壤环境与抗生素耐药性

土壤是耐药菌在人、牲畜、农作物之间流动的媒介[45]。研究人员从农业土壤、城市土壤、自然土壤中都分离出多重耐药菌[46]。抗生素可以通过直接施用和动物粪便进入农田土壤环境。在美国，每年有 70 t 抗生素用于农作物种植[47]。变形杆菌等土壤微生物可从大肠埃希菌中捕获耐药质粒，并促进耐药质粒传播至植物微生物[48]。废水灌溉也促进了耐药微生物和耐药基因向环境中的传播[49]。废水灌溉虽然对土壤微生物群落密度或组成无影响，但废水灌溉田的抗生素耐药基因丰度更高，而且丰度与灌

溉强度呈正相关[50]。人类医疗废物的填埋不仅会增加土壤中抗生素耐药基因的丰度和多样性，也会增加土壤中的金属离子浓度，成为抗生素耐药性的协同选择压力[51]。

1.3.2 水环境与抗生素耐药性

水环境是微生物最重要的栖息地之一，也是微生物在自然界中迁移的重要媒介，是公认的抗生素耐药基因储存库[52-54]。耐药基因可以在人、动物、家庭饮用水和公共水源中流动[55]。饮用水中就存在着多种抗生素耐药基因及其水平转移现象[56]。城市污水处理厂也是耐药菌和耐药基因交换的场所[57]，污水处理无法完全去除耐药基因，氧化还原净水反而会增加抗生素耐药基因的水平转移[58-59]。

1.3.3 空气微粒与抗生素耐药性

抗生素耐药基因，尤其是耐碳青霉烯酶基因可以通过医院和社区环境中的 $PM_{2.5}$ 和 PM_{10} 传播[60]。家庭[61]、学校、幼儿园[62]等室内场所的空调过滤器灰尘或空气中也存在耐药微生物和耐药基因。抗生素耐药基因还可以吸附在城市扬尘、污水处理厂和垃圾焚烧厂的气溶胶中进入大气，通过气流运动实现全球传播[63]。同时这些气溶胶也可以通过雨雪沉积返回地面，实现抗生素耐药性的循环[64]。

2 全健康视角下的抗生素耐药性传播与控制

运用“全健康”的理念和方法整合人、动物和环境中微生物耐药性传播途径特征，增强研究者对抗生素耐药性复杂流行病学的理解，从而调动多学科、多部门协作，遏制抗生素耐药性传播,解决人-动物-环境界面的抗生素耐药性问题[65]。

2015 年，世界卫生组织、联合国粮农组织(Food and Agriculture Organization of the United Nations，FAO)和世界动物卫生组织(Office International Des Epizooties，OIE)三方联合发起了《抗微生物药物耐药性全球行动计划》，该计划要求所有国家都通过多部门协调来实施国家行动方案，以确保在人类、动物和环境领域进行全面监测、治理和政策实施。世界卫生组织不断帮助各国建立或完善国家抗生素耐药监测系统，并为国际、区域、国家和组织之间的密切合作提供更全面的标准化抗生素耐药性监测数据[66]。欧盟(European Union，EU)下属的欧洲药品管理局(European Medicines Agency，EMA)、欧洲疾病控制中心(European Centre for Disease Prevention and Control，ECDC)和欧洲食品安全局(European Food Safety Authority，EFSA)等机构在 2017 年制定《欧盟针对抗生素耐药性的“全健康”行动计划》[67]，通过欧洲抗生素消费监测网(European Surveillance of Antimicrobial Consumption Network，ESAC-Net)[68]和欧洲兽用抗生素消费监测项目(European Surveillance of Veterinary Antimicrobial Consumption，ESVAC)[69]对整个欧盟医疗用抗生素和养殖用抗生素的使用进行监管，联合公布各行业抗生素使用数据，并证实了动物中应用抗生素与人体产生耐药基因呈正相关，明确了减少抗生素使用的必要性[70-71]。2020 年，瑞典发布了《瑞典 2020−2023 年抗击抗生素耐药性战略》[72]，该计划再次强调了抗生素耐药性在人、动物和环境之间传播的复杂性，该战略既侧重医疗和兽医、农业和环境等多部门之间的合作，又加强 EU、OIE、WHO、FAO 和经合组织(Organization for Economic Co-operation and Development，OECD)之间的合作[73]，具有典型的“全健康”理念特色。虽然国际上已经就使用“全健康”理念解决抗生素耐药性问题达成一致[2]，许多国家、地区和国际组织都启动了遏制抗生素耐药性的国家计划，但

这一行动需要更多国家，尤其是在医疗领域和养殖动物中使用非处方抗生素缺乏监管的发展中国家参与(表 1)。

2016 年, 中国国家卫健委等 14 个部门联合制定《遏制细菌耐药国家行动计划(2016−2020 年)》, 该计划不仅完善了临床和养殖业的抗生素应用和细菌耐药的监测网络，还加强了对水、土壤等环境中抗生素污染的监测，实现农林畜牧业和水产养殖业的联防联动[74]。2021 年中国细菌耐药监测网(China Antimicrobial Surveillance Network，CHINET)的监测结果显示，在甲氧西林耐药的细菌中，金黄色葡萄球菌检出率由 2016 年的 38.4%下降至 30.0%，而检出率处于高位的表皮葡萄球菌未发现针对万古霉素、去甲万古霉素和替加环素的耐药菌株，其他凝固酶阴性的葡萄球菌(检出率为 77.7%)中也未发现针对万古霉素和替加环素的耐药菌株；铜绿假单胞菌、鲍曼不动杆菌和耐碳青霉烯肺炎克雷伯菌对硫酸粘菌素仍高度敏感。目前，我国各地区的医院、养殖场的耐药监测水平参差不齐，影响监测网络中的数据质量，而且各个监测网之间存在“信息孤岛”现象。因此，“全健康”理念下战略部署和整合现有平台来监管“人-动物-环境”中的耐药性显得尤为重要。

3 总结与展望

各种人类活动促进抗生素耐药性在人-动物-环境界面的流动与循环，“全健康”理念是解决这一复杂而又隐匿传播的有效策略。目前，将“全健康”政策应用于遏制抗生素耐药性的行动仍然处于全球倡议、区域合作的起步阶段，“全健康”治理的碎片化问题仍然突出。

我们倡导更多的国家和地区应用“全健康”方法控制抗生素耐药性传播，通过减少在食用动物养殖中使用人类医疗中发挥重要作用的抗生素，禁止以促进养殖动物生长为目的长期在饲料中使用抗生素，在人群中通过预防感染以减少过度使用抗生素，加强个人卫生和饮用水

表 1 全球不同国家、地区和国际组织遏制抗生素耐药性的行动

Table 1 Global action by countries, regions and international organizations to curb antibiotic resistance

国家或地区 Country or region	年份 Year	负责或发起部门 Responsible or initiating department	项目或文件 Projects or policies	参考文献 References
中国 China	2016	中国国家卫健委等 14 个部门 National Health Commission of the People’s Republic of China and 14 other departments	遏制细菌耐药国家行动计划(2016–2020 年) National Action Plan for Containing Antibacterial Resistance (2016–2020)	[74]
美国 U. S.	1996	美国食品和药物管理局的兽药中心，美国农业部和美国疾病预防控制中心 U.S. Food and Drug Administration Center for Veterinary Medicine (FDA/CVM), U. S. Department of Agriculture (USDA), and U.S. Centers for Disease Control and Prevention (CDC)	国家抗生素耐药监测系统 National Antimicrobial Resistance Monitoring System (NARMS)	[75]
	2020	总统科学技术顾问委员会 President’s Council of Advisors on Science and Technology	遏制抗生素耐药细菌国家行动计划 National Action Plan for Combating Antibiotic-Resistant Bacteria	[76]

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(续表 1)

加拿大 Canada	2017	加拿大政府和多所学术机构、非政府组织 Government of Canada and multiple academic institutions, non-governmental organizations	应对抗生素耐药性和抗生素使用：泛加拿大行动框架 Tackling antimicrobial resistance and antimicrobial use: a Pan-Canadian framework for action	[77]
欧盟 European Union	2009	欧洲食品安全局和欧洲疾病预防和控制中心 European Food Safety Authority (EFSA) and European Centre for Disease Prevention and Control (ECDC)	欧洲兽用抗生素消费监测项目 European Surveillance of Veterinary Antimicrobial Consumption (ESVAC)	[68]
	2010	欧洲疾病预防和控制中心 European Centre for Disease Prevention and Control (ECDC)	欧洲抗生素耐药性监测网络 European Antimicrobial Resistance Surveillance Network (EARS-Net)	[78]
	2011	欧洲药品管理局和欧洲疾病预防和控制中心 European Medicines Agency (EMA) and European Centre for Disease Prevention and Control (ECDC)	欧洲抗生素消费监测网 European Surveillance of Antimicrobial Consumption Network (ESAC-Net)	[69]
	2012	欧洲疾病预防和控制中心 European Centre for Disease Prevention and Control (ECDC)	欧洲食源性和水源性疾病和人畜共患病网络 European Food- and Waterborne Diseases and Zoonoses Network (FWD Net)	[79]
	2017	欧盟委员会 European Commission	欧盟针对抗生素耐药性的“全健康”行动计划 European One Health Action Plan against antimicrobial resistance	[67]
瑞典 Sweden	2020	瑞典卫生和社会事务部 Swedish Ministry of Health and Social Affairs	瑞典 2020–2023 年抗击抗生素耐药性战略 Swedish strategy to combat antibiotic resistance 2020–2023	[72,80]
荷兰 Netherlands	2015	荷兰卫生、福利和体育部 Ministry of Health, Welfare and Sport of the Netherlands	医疗领域抗生素耐药性管理协议 Administrative agreements on antibiotic resistance in healthcare	[81]
比利时 Belgium	2013	比利时抗生素政策协调委员会 Belgian Antibiotic Policy Coordination Commission (BAPCOC)	2014–2019 年第三个抗击抗生素耐药性的国家战略计划 The third National Strategic Plan to fight against antimicrobial resistance 2014–2019	[82]
英国 United Kingdom	2013	英国卫生部 UK Department of Health	2013–2018 年英国抗生素耐药性的国家战略 UK 5 Year Antimicrobial Resistance Strategy 2013 to 2018	[83]
法国 France	2011	法国劳动、就业和卫生部 French Ministry of Labour, Employment and Health	法国国家抗生素预警计划(2011–2016) Plan national d'alerte sur les antibiotiques 2011–2016 National alert plan on antibiotics 2011–2016	[84]
澳大利亚 Australia	2015	澳大利亚农业部和卫生部 Australian Department of Agriculture and Department of Health	2015−2019 年国家抗生素耐药性战略 National Antimicrobial Resistance Strategy 2015–2019	[85]

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(续表 1)

印度 India	2012	印度疾病预防控制中心 Indian National Centre for Disease Control	遏制抗生素耐药性国家计划(2012–2017 年十二五规划内 National Programme for the Containment of Antimicrobial Resistance (within the 12th Five Year Plan, 2012–2017)	[86]
	2012	印度医学研究理事会 Indian Council of Medical Research	抗生素耐药性监测研究网络 Antimicrobial Resistance Surveillance Research Network	[87]
	2017	包括卫生、环境、农业和粮食在内的 12 个部委 India's 12 ministries, including health, environment, agriculture and food departments	抗生素耐药性国家行动计划 The National Action Plan on Antimicrobial Resistance 关于抗生素耐药性的德里宣言 The Delhi Declaration on AMR	[88-89]
越南 Vietnam	2012	越南国家卫生部、越南传染病学会、牛津大学临床研究会和瑞典林雪平大学合作 Collaboration between the Vietnamese Minister of Health, the Vietnamese Infectious Diseases Society, the Oxford University Clinical Research Unit and Linköping University in Sweden	越南抗生素耐药性控制项目 Viet Nam Resistance (VINARES) Project	[90]
泰国 Thailand	1997	泰国国家卫生研究院 the National Institutes of Health in Thailand	泰国国家卫生研究院国家抗生素耐药性监测中心 National AMR Surveillance Center at the National Institutes of Health	[91]
非洲地区 Africa	2002	美国国际开发署、美国疾病预防控制中心的 IDSR 团队与世卫组织/非洲区域办事处合作 Collaboration between United States Agency for International Development (USAID), CDC's Integrated Disease Surveillance and Response team and the WHO/Africa Regional Office (WHO/AFRO)	非洲综合疾病监测和应对 AFRO Integrated Disease Surveillance and Response (IDSR)	[92]
肯尼亚 Kenya	2017	肯尼亚国家抗生素管理咨询委员会 Kenya National Antimicrobial Stewardship Advisory Committee	预防和控制抗生素耐药性国家政策 National Policy on Prevention and Containment of AMR	[93]
南非 South Africa	2015	南非国家卫生部 South African National Department of Health	抗生素耐药性-国家战略框架(2014–2024)和抗生素耐药性战略框架实施计划(2014–2019) Antimicrobial resistance. National strategy framework 2014–2024. And implementation plan for the antimicrobial resistance strategy framework in South Africa, 2014–2019	[94]
拉丁美洲地区 Latin America	1996	泛美卫生组织/世界卫生组织美洲地区办事处及其成员国 Pan American Health Organization/World Health Organization Regional Office for the Americas (PAHO/AMRO) and its member countries	拉丁美洲抗生素耐药性监测网络 Red Latinoamericana de Vigilancia a las Resistencias Antimicrobianas (ReLAVRA) Latin American Network for Antimicrobial Resistance Surveillance	[95]

等卫生设施，加强环境污物治理来阻止抗生素耐药微生物的快速传播，并通过改进监测、药物管理、感染控制、医疗卫生、畜牧业和寻找抗微生物药物的替代品等多部门协同合作来应对抗生素耐药性的全球挑战，促进人类健康、动物健康和生态环境协调发展。

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