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Title: Rational use of tuberculosis drugs to prevent the development of drug resistance

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Body: The tuberculosis (TB) drug pipeline has finally thickened and several new agents are under clinical development. We assessed risks related to the introduction of new drugs and the development of drug-resistance with the aim to support stakeholders when introducing new drugs and regimens in TB Programs. Using standardised Cochrane and PRISMA Guidelines systematic reviews were conducted. We assessed; how often TB patients are prescribed inadequate drug regimens; the knowledge of healthcare workers (HCW) on TB regimens; and the risk of developing multi-drug resistant TB (MDR-TB) when an inappropriate regimen was prescribed. A questionnaire was developed by ECDC and ERS to map national Community Acquired Pneumonia (CAP) guidelines and the risk of fluoroquinolone (FQ) resistant TB after treatment for CAP was assessed. Between 0.4% and 100% of TB patients were prescribed an inadequate regimen. Between 8% and 100% of HCW reported having inappropriate knowledge of TB regimens. The risk for MDR-TB after being prescribed an inappropriate regimen increased by 27-fold (26.7, 95% CI 5.0-141.7). In the EU/EEA, 18 countries had CAP guidelines, of which two recommended FQ as the first drug for CAP treatment. Treatment with FQ before TB diagnosis resulted in a three-fold higher risk of having FQ resistant TB (OR 2.81, 95% CI 1.47-5.39). These studies provide evidence that TB drugs are prescribed in inadequate regimens and that inadequate regimens, or the use of FQ for CAP, present an increased risk of drug-resistance. There is an urgency to strengthen guidelines and adherence to these to ensure a rational use of TB drugs and prevent the further development of resistant TB.