25 March 2015
EMA/201512/2015

EU Medicines Agencies Network Strategy to 2020 - Working together to improve health

Submission of comments

Comments from:

Name of organisation or individual
Dr Rachael Liebmann Registrar Royal College of Pathologists with contributions from Riina Richardson and Rosemary Barnes Fellows of the RCPath

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received. In your reply please indicate whether you are replying as a citizen, organisation or public authority.

Comments should be sent to the European Medicines Agency electronically and in Word format (not pdf).

Comments should be sent to EUnetworkstrategy@ema.europa.eu and must arrive by 30 June 2015.

General comments

General comment (if any)	Outcome (if applicable) *<to be completed by the EMA/HMA>*
In general Fellows of the Royal College of Pathologists welcomed this consultation and the initiative it represents.	

Specific comments on text

Line No. of the first line(s) affected	Comment and rationale; proposed changes	Outcome (if applicable) *<to be completed by the EMA/HMA>*
	Concerns were expressed about whether fungal pathogens and antifungal resistance had been considered and included. This clearly links with agricultural use of azoles as a risk factor. Another but more global concern is that after ketoconazole lost its licence there are no mould active oral antifungals on the WHO[1]s essential medicines list. Co-infection with TB is very common in many countries and lungs with TB cavities are at very high risk of developing chronic aspergillosis with high annual mortality in the absence of treatment. Resistance to antifungal agents is a growing global problem that requires urgent attention. The impact of agricultural and horticultural use of antifungals is not considered.	

Line No. of the first line(s) affected	Comment and rationale; proposed changes	Outcome (if applicable) *<to be completed by the EMA/HMA>*
	Tri-azole antifungal agents are the mainstay of treatment for invasive fungal infections and in the absence of effective treatment these infections are lethal. Tri-azoles also offer the most cost effective approach, and antifungal stewardship programmes aim at restricting their unnecessary use in order to spare their activity. At the same time, azole fungicides are widely used for crop protection and material preservation. Millions of kilograms of tri-azole agents are used in the regular spraying of crops and food commodities in the Europe each year. Despite this, fungi continue to decimate major food crops such as wheat, and barley.(1) The recent flooding and global disasters are likely to result in an increased need for fungicides as environmental disruption triggers dispersion and moist conditions promote fungal growth.(2) Ongoing climactic change and global warming exacerbate the problem.(3) This is relevant to human disease as the main source for human fungal pathogens is the environment. Azole resistance in one of the most important fungal pathogens, *Aspergilllus fumigatus,* has emerged rapidly over the last decade and this has been clearly linked to azole fungicide use in agriculture.(4) The prevalence of aspergillosis is not clearly defined and although invasive disease is rare and confined to immunocompromised populations, the burden of chronic respiratory disease in terms of asthma, allergic bronchopulmonary aspergillosis and chronic pulmonary aspergillosis affects millions of individuals worldwide.(5) Improvements in medical care have resulted in a growing population of immunocompromised patients at risk for severe fungal infections. There is strong evidence that antifungal resistance results in clinical failure and higher mortality rates (6, 7). Azole resistance of *Aspergillus* was first noted in the 1990's and	

Line No. of the first line(s) affected	Comment and rationale; proposed changes	Outcome (if applicable) *<to be completed by the EMA/HMA>*
	has risen steadily since.(7, 8) Early cases were shown to arise from a variety of de novo mutations in patients on long-term therapy for chronic respiratory conditions. However, more recently a clonal resistance mechanism has been identified in both patient and environmental isolates. Whilst most prevalent in the Netherlands, it has now spread globally(9-13)and represents a significant public health problem.(14) This specific TR34/L98H mutation consists of a tandem repeat of 34 bases (TR34) within the promotor region of the CYP51A gene, combined with a leucine to histidine amino acid substitution (L98H). Azole resistance is found in up to 26% of environmental surveillance isolates in Europe and in TR34/L98H mutation is present in 50% of these.(4) Interestingly, the TR34/L98H mutation has not been the most frequently reported resistance mechanism in the UK but this should be interpreted with caution as data are extremely limited. (15) Importantly, this TR34/L98H mutation linked resistance is not only found in environmental isolates of *Aspergillus* but also in clinical isolates from patients with no previous azole antifungal exposure. It appears that the patients have become infected with an azole resistant environmental strain. The mutation confers pan-azole resistance to itraconazole, voriconazole, posaconazole(16) as well as many azoles widely used in agriculture. Global spread of this resistance mechanism has been linked to the selective pressures exerted by massive agricultural fungicide usage. (17) Whilst direct evidence linking resistance to pesticide use is lacking, the circumstantial evidence is overwhelming.(16, 18) Recently, another environmental mechanism of resistance has been identified and associated with clinical treatment failures in patients. (17) This too has been linked to agricultural use of fungicides and highlights the need for the medical and mycological establishment to invest in robust	

Line No. of the first line(s) affected	Comment and rationale; proposed changes	Outcome (if applicable) *<to be completed by the EMA/HMA>*
	surveillance and identify azole resistance as a research priority. Recent analysis has highlighted that mycology in the UK receives only 2% of funding allocated for research in human infectious diseases.(19) Little of this is directed at global health and translational research is relatively poor. However a lack of investment and succession planning remain and this coincides with the burgeoning problems of antifungal drug resistance, emerging infections and increasing antifungal drug expenditure as well as increased morbidity and mortality. 1. Control ECfDPa. Risk assessment on the impact of environmental usage of triazoles on the development and spread of resistance to medical triazoles in Aspergillus species. In: Stockholm E, editor. Stockholm: ECDC Stockholm; 2013. 2. Benedict K, Park BJ. Invasive Fungal Infections after Natural Disasters. Emerg Infect Dis 2014(Mar). 3. Garcia-Solache MA, Casadevall A. Global Warming Will Bring New Fungal Diseases for Mammals. Mbio. 2010;1(1). 4. Chowdhary A, Kathuria S, Xu J, Meis JF. Emergence of azole-resistant *Aspergillus fumigatus* strains due to agricultural azole use creates an increasing threat to human health. PLOS Pathogens. 2013;9(10):e1003633. 5. Brown GD, Denning DW, Gow NAR, Levitz SM, Netea MG, White TC. Hidden Killers: Human Fungal Infections. Sci Transl Med. 2012;4(165):165rv13. 6. Arendrup MC, Mavridou E, Mortensen KL, Snelders E, Frimodt-Moller N, Khan H, et al. Development of Azole Resistance in Aspergillus fumigatus during Azole Therapy Associated with Change in Virulence. Plos One. 2010;5(4). 7. Howard SJ, Cerar D, Anderson MJ, Albarrag A, Fisher MC, Pasqualotto AC, et al. Frequency and Evolution of Azole Resistance in Aspergillus fumigatus Associated with Treatment Failure. Emerg Infect Dis. 2009;15(7):1068-76. 8. Mortensen KL, Jensen RH, Johansen HK, Skov M, Pressler T, Howard SJ, et al. Aspergillus Species and Other Molds in Respiratory Samples from Patients with Cystic Fibrosis: a Laboratory-Based Study with Focus on Aspergillus fumigatus Azole Resistance. J Clin Microbiol. 2011;49(6):2243-51. 9. Astvad KMT, Jensen RH, Hassan TM, Mathiasen EG, Thomsen GM, Pedersen UG, et al. First Detection of TR46/Y121F/T289A and TR34/L98H Alterations in Aspergillus fumigatus Isolates from Azole-Naive Patients in Denmark despite Negative Findings in the Environment. Antimicrob Agents Chemother. 2014;58(9):5096-101.	

Line No. of the first line(s) affected	Comment and rationale; proposed changes	Outcome (if applicable) *<to be completed by the EMA/HMA>*
	10. Bader O, Weig M, Reichard U, Lugert R, Kuhns M, Christner M, et al. cyp51A-Based Mechanisms of Aspergillus fumigatus Azole Drug Resistance Present in Clinical Samples from Germany. Antimicrob Agents Chemother. 2013;57(8):3513-7. 11. Lockhart SR, Frade JP, Etienne KA, Pfaller MA, Diekema DJ, Balajee SA. Azole Resistance in Aspergillus fumigatus Isolates from the ARTEMIS Global Surveillance Study Is Primarily Due to the TR/L98H Mutation in the cyp51A Gene. Antimicrob Agents Chemother. 2011;55(9):4465-8. 12. Seyedmousavi S, Hashemi SJ, Zibafar E, Zoll J, Hedayati MT, Mouton JW, et al. Azole-Resistant Aspergillus fumigatus, Iran. Emerg Infect Dis. 2013;19(5):832-4. 13. Steinmann J, Hamprecht A, Vehreschild MJGT, Cornely OA, Buchheidt D, Spiess B, et al. Emergence of azole-resistant invasive aspergillosis in HSCT recipients in Germany. The Journal of antimicrobial chemotherapy. 2015;70(5):1522-6. 14. Vermeulen E, Lagrou K, Verweij PE. Azole resistance in Aspergillus fumigatus: a growing public health concern. Current Opinion in Infectious Diseases. 2013;26(6):493-500. 15. Fraczek MG, Bromley M, Buied A, Moore CB, Rajendran R, Rautemaa R, et al. The cdr1B efflux transporter is associated with non-cyp51a-mediated itraconazole resistance in Aspergillus fumigatus. J Antimicrob Chemother. 2013;68(7):1486-96. 16. Snelders E, Camps SMT, Karawajczyk A, Schaftenaar G, Kema GHJ, van der Lee HA, et al. Triazole Fungicides Can Induce Cross-Resistance to Medical Triazoles in Aspergillus fumigatus. Plos One. 2012;7(3). 17. Verweij PE, Snelders E, Kema GHJ, Mellado E, Melchers WJG. Azole resistance in Aspergillus fumigatus: a side-effect of environmental fungicide use? Lancet Infectious Diseases. 2009;9(12):789-95. 18. Stensvold CR, Jorgenson LN, Arendrup MC. Azole-resistant invasive aspergillosis: relationship to agriculture. Curr Fungal Infect Rep. 2012;6:178-91. 19. Head MG, Fitchett JR, Atun R, May RC. Systematic analysis of funding awarded for mycology research to institutions in the UK, 1997-2010. BMJ Open. 2014;4(1):6.	