Adverse Event Management in Mass Drug Administration for Neglected Tropical Diseases

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ABSTRACT

The ethical challenges of reporting and managing adverse events (AEs) and serious AEs (SAEs) in the context of mass drug administration (MDA) for the treatment of neglected tropical diseases (NTDs) require reassessment of domestic and international policies on a global scale. Although the World Health Organization has set forth AE/SAE guidelines specifically for NTD MDA that incorporate suspected causality, and recommends that only SAEs get reported in this setting, most regulatory agencies continue to require the reporting of all SAEs exhibiting even a merely temporal relationship to activities associated with an MDA program. This greatly increases the potential for excess "noise" and undue risk aversion and is not only impractical but arguably unethical where huge proportions of populations are being treated for devastating diseases, and no good baseline exists against which to compare possible AE/SAE reports. Other population-specific variables that might change the way drug safety ought to be assessed include differing efficacy rates of a drug, background morbidity/mortality rates of the target disease in question, the growth rate of the incidence of disease, the availability of rescue or salvage therapies, and the willingness of local populations to take risks that other populations might not. The fact that NTDs are controllable and potentially eradicable with well-tolerated, effective, existing drugs might further alter our assessment of MDA safety and AE/SAE tolerability. At the same time, diffuseness of population, communication barriers, lack of resources, and other difficult surveillance challenges may present in NTD-affected settings. These limitations could impair the ability to monitor an MDA program's success, as well as hinder efforts to obtain informed consent or provide rescue therapy. Denying beneficial research interventions and MDA programs intended to benefit millions requires sound ethical justification based on more than the identification of and rote response to AEs and SAEs. (*Clin Ther*. 2014;36:421–424)

Key words: adverse events, benefit, developing nation, research ethics, risk.

INTRODUCTION

The reporting and management of adverse events (AEs) and serious AEs (SAEs) are considered crucial components of human subjects' protection and pharmacosurveillance. For both practical and ethical reasons, however, it is essential to strive for an appropriate signal-to-noise ratio when reporting and managing AEs and SAEs. This requires setting appropriate domestic and international policies for addressing AE/SAE concerns. Applying these considerations to mass drug administration (MDA) for the prevention of neglected tropical diseases (NTDs) is particularly challenging. In many instances there is no baseline against which to compare reports of possible AEs. In other instances the level of adversity introduced by the widespread use of a drug or vaccine is minimal relative to the benefit produced.

More than 1 billion people in the world's most vulnerable populations suffer from one or more NTDs, many of which result in severe disfigurement, disability, or death.[1] The core 13 NTDs comprise: (1) protozoan infections (human African trypanosomiasis, Chagas disease, and leishmaniasis); (2) bacterial infections (Buruli ulcer, leprosy, and trachoma); and (3) helminthic infections (ascariasis, trichuriasis, schistosomiasis, lymphatic filariasis, onchocerciasis, and dracunculiasis).[2] These diseases kill a half-million people per year, most of whom live on less than US $2 per day.[1] The combined global burden of

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NTDs has been estimated at 56.6 disability-adjusted life years (DALYs), a burden greater than that of both tuberculosis (34.7 DALYs) and malaria (46.5 DALYs) and approaching that of HIV/AIDS.[2] Even so, arguments for upward revision of NTD disability weightings are frequently made, predicated on a variety of rationales. For example, the global prevalence of schistosomiasis has been estimated at 200 million, but the stool and urine tests giving rise to this figure are so insensitive that it is thought to be much higher.[2] Additionally, serious conditions such as bladder and liver fibroses may result from childhood schistosomiasis infections but fail to be properly attributed to their NTD root cause because they occur much later in life.[2] Urogenital schistosomiasis can lead to cervical lesions that increase HIV contraction rates in young women.[2] More indirect or subtle morbidity effects of these types compound the underestimation of the impact of NTDs on human health.

Fortunately, 7 of the most prevalent NTDs can be controlled with mass drug administration (MDA) of preventive chemotherapy.[1] Because these treatments are administered to hundreds of millions of people, striking the appropriate signal-to-noise ratio is crucial to ensuring maximal treatment and disease control while properly managing associated AEs and SAEs. The standard World Health Organization (WHO) definition of an AE is "any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment."[3] SAEs can be defined as those that: (1) are life-threatening or fatal; (2) cause or prolong hospital admission; (3) cause persistent incapacity or disability; or (4) concern misuse or dependence.[3] Because reporting all AEs/SAEs under these standard definitions would capture so many hospitalizations, deaths, and other events that were temporally but not necessarily causally associated with an interventional drug in the MDA setting, WHO has set forth guidelines for AEs/SAEs specifically following preventive chemotherapy that require suspected causality and recommend that only SAEs get reported.[3] This responds to the concern that too much ongoing disease "noise" could easily overwhelm MDA and in the worst case could lead to the cessation of a highly beneficial MDA program. However, most North American regulatory agencies continue to require the reporting of all SAEs exhibiting even a merely temporal relationship to activities associated with an MDA program. This is not only impractical in many situations but also arguably unethical in a context in which 80% of populations are afflicted with a variety of highly prevalent and devastating diseases, and no good baseline exists against which to compare possible AE/SAE reports. Penalizing MDA efforts for underlying issues of poor health reduces the availability of MDA efforts for at-risk populations.

The world's experience with the rotavirus vaccine is illustrative of an overemphasis on small rates of AEs in analyzing MDAs and mass vaccination efforts. Rotavirus causes an estimated 500,000 diarrhea-related deaths (85% of which occur in Africa and Asia), and 2 million child hospitalizations, worldwide each year.[4] Two rotavirus vaccines, one pentavalent* and one monovalent,† have been available to prevent the disease since 2006 and 2008, respectively.[5] The first available rotavirus vaccine‡ was approved by the US Food and Drug Administration and released in 1998 but was withdrawn from the market in 1999,[6] after ~1 million children had received it, when the Centers for Disease Control and Prevention suspended its recommendation of the vaccine due to an increase in intussusception cases among children who had received it. As to the extent of the risk, the Centers for Disease Control and Prevention estimated that merely "one or two additional cases of intussusception would be caused among every 10,000 infants vaccinated with [the] vaccine."[7] Thus, the withdrawal of the first rotavirus vaccine from the market because of a *possible* very low increased risk for an SAE—a risk deemed unacceptably high in the United States—led to a 7-year gap during which no approved vaccine existed to prevent a disease that killed 3.5 million people in that same period. Moreover, the cost of the vaccines that finally became available is extremely high and therefore they are still inaccessible to many infants and children who need them most. Due to the intense scrutiny that accompanied this debacle—since

*Trademark: Rotateq® (Merck Sharp & Dohme, Whitehouse Station, New Jersey).

†Trademark: RotaRix® (GlaxoSmithKline, Research Triangle Park, North Carolina).

‡Trademark: RotaShield® (Wyeth Pharmaceuticals, Madison, New Jersey).