

REPLY LETTER

## Reply letter and clarifications on behalf of La Rosa and colleagues to Sicilian Public Health Authorities

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### ABSTRACT

In May 2016 we published in the journal *Human Vaccines and Immunotherapy*. 1 79 80 the case-report “Post-rotavirus vaccine intussusception in identical twins: a case report.” We received a reply letter from “Sicilian Public Health Authorities” that placed attention to some points of our work. We would like to do some clarifications.

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Dear sirs,

We read with great interest the remarks of some of the statements contained in our work “Post-rotavirus vaccine intussusception in identical twins: a case report” recently published in *Human Vaccines and Immunotherapy*.<sup>1</sup>

We would like to make it clear that we recognize the huge importance and usefulness of vaccinations for the public health. Particularly we recognize the benefits obtained with the introduction of universal vaccination against Rotavirus<sup>2-5</sup>: an improvement in world pediatric health especially for the pre-term and/or low birth weight newborns and for those affected by congenital diseases.<sup>2,6,7</sup> We also appreciate the benefits that the Rotavirus vaccine has had for Sicilian population since its introduction in 2012<sup>8</sup> and we recognize the important work done by all the Sicilian institutions for observation and epidemiological analysis on infections in our area.<sup>9</sup>

We are aware as a single case-report is not enough to change the policy of vaccination, and this is not the goal of our publication. We would like to clarify that our paper reports 2 cases of intussusception characterized by 2 significant peculiarity: the identical twins and the proximity to the Rotavirus vaccine. As evidenced by the literature in fact the intussusception can be a side effect of Rotavirus vaccine even if rare.<sup>1-2,10-12</sup>

The only intent of our work is to arouse curiosity for intussusception cases and their relation with Rotavirus vaccine, to consider the usefulness of additional studies but, above all, to emphasize the importance of a clinic case that could evoke possible genetic factors predisposing to the intussusception whose evidences are not many.

We want to clarify our full confidence in the functioning of our regional health system, in particular of the Sicilian institutions for control of vaccines campaign. We are aware that pediatricians of the health system of Sicily have all the tools to

make the best possible choices about vaccination of their patients.

However we believe that this is not in conflict with the possibility and the duty of every healthcare worker to report events of its everyday practice especially if they could be useful to recognize and to treat life-threatening conditions such as intussusception. We in our paper wanted to specifically point out the possible advantage in the early detection of the disease thanks to a quick family history. For our experience of doctors working in an emergency department, this information may be helpful especially for the purpose of differential diagnosis. It can lead to a possible reduction of the timing for the diagnosis and for the surgical treatment.<sup>13</sup> We chose a wide-distribution journal also because we believe that it could be useful to analyze our topic also comparing it with any similar findings in different realities beyond Sicily. In fact, although in the era of Evidence Based Medicine (EBM) the randomized clinical trial corresponds to the highest step in the qualitative scale of the evidence available in the literature, is undeniable as case-reports have significantly contributed to the advancement of scientific knowledge. The case reports often are only the first evidence of a new clinical situation. While not representing a thorough paper, it is often the main source of information about adverse and/or rare cases events.

We want to clarify some points that we consider worthy of discussion:

1. We confirm that the children birth date was on June 2013 and that they were born at 36+0 weeks of gestational age. We immediately proceeded to report the error to the competent offices even before your replay letter. However we are not agree with your sentence “the pre-term condition might act as a confounding factor to the occurrence of intussusception” [cit. Vitale’s et al. Replay

letter]. The intussusception is an extremely rare event in the preterm newborn in which it probably has a different etiopathogenesis than in the term babies.<sup>14-15</sup> We was not able to detect any scientific evidence that affirm that prematurity is a risk factor for intussusception even in the cases related to the Rotavirus vaccine. Preterm newborns are instead a target population for Rotavirus vaccination due to a much favorable cost/benefit rate.<sup>6</sup>

2. We confirm that the vaccine administration was done in September 2013 and not in 2014. The twins underwent the oral monovalent life-attenuated Rotavirus vaccination (RV1) at 3 months of age and within 24 weeks of age. So, it was not an off label administration.<sup>16</sup> We thank the authors for pointing out our error.
3. Yes, the sentence “on the advice of pediatrician”<sup>1</sup> implied that he/she followed the Regional Immunization Schedule. We are extremely confident in its effectiveness for verifying the absence of vaccine contraindication in babies and children and counseling the families for a consciousness adherence to the vaccination program.
4. The association between the RV1 or the pentavalent human-bovine reassortant Rotavirus vaccine (RV5) and the intussusception inspired many scientific works, the newest was published on June 2016.<sup>2,6,12</sup> Further researches on this topic are certainly necessary and we consider very appropriate your case-control trial started in January 2016. The actual scientific evidences state that the intussusception is a rare but possible adverse event of the Rotavirus vaccine. However the low-risk of vaccination-associated intussusception is outweighed from the many benefits of vaccination.<sup>6,12</sup> All of the above was already written in our work “It is reasonable to conclude that intussusception can occur with either vaccine, but that the risk is low, on the order of 1–5 cases per 100,000 infants, therefore the benefit-risk balance for Rotarix<sup>TM</sup> and RotaTeq<sup>®</sup> is favorable. From a public health perspective, the benefits in terms of prevented RVGE hospitalizations and deaths for the vaccinated population far exceed the estimated risks due to intussusception”[1]. We know and we are very proud for the very effective Sicilian surveillance program on this topic but our obvious but useful advice about the monitoring of the cases of intussusception was open to all healthcare professionals who read our article, even outside of Sicily.
5. The intussusception is probably a multifactorial disease.<sup>17</sup> We know that there are not prospective and randomized studies about familiarity in vaccination-associated intussusception. However there are many descriptions of familiar intussusception cases as we learned from a literature review of more than 15 studies published in 2007.<sup>13</sup> In the same paper the incidence of familial intussusception was estimated to be 1 in 14.2 cases.<sup>13</sup> Despite in our case-report the concordance of the genotype in monozygotic twins and the lack of a suggestive family history could not allow us to speak of “suspected familial disease” for our patients, we believe it would certainly be interesting to continue surveillance for their family at least until the subsequent generation. At date, there are not proved genotype-phenotype correlation for intussusception.

Nevertheless we believe the presence of the same pathology in both identical twins is worth considering because it could reveal a genetic predisposing factor to the disease. So we take advantage of this reply letter to reiterate that a comprehensive study of the genome of both twins and a general survey on the presence of new similar cases in other countries could be helpful.<sup>13,18-20</sup> Then we wait with interest for the results of your study started in 2016.

6. We confirm that in our paper we did not report that the twins underwent cephalosporins administration 2 d before their hospitalization. Even if this is indicated such as another possible risk factor for intussusception, we found only 3 studies about this topic in childhood.<sup>21-22,24</sup> Moreover Spiro’s studies of 2003 and of 2005 have some limits: the first is a retrospective, non-blinded study in which the informations rely on handwritten medical records while the second is an animal study with poor statistical significance for the few number of cases observed (4 cases in exposed mice versus no cases in unexposed mice).<sup>21-22</sup> The Danish study published in 2009 concerns mainly the broad-spectrum penicillins and the macrolides. The authors declare that their study cannot evaluate the cephalosporins effects because this class of antibiotic is very little used in the Danish pediatric population.<sup>23</sup> A relation between this class of antibiotics and the intussusception is instead demonstrated in a case-cross-over study of the 2015 in which cephalosporins represent the 58% of the prescribed antibiotic. This work reports a Global Effect Odds Ratio (95% CI) of 2.00 (0.60–6.64) related to the antibiotic administration 2 d before the intussusception in children younger than 2 y. However also this study presents some limits and requires other multi-centric, controlled studies. Certainly further studies are needed to correlate asthma medicine with intussusception.<sup>22,24</sup>

We conclude reiterating that the last sentence of our paper “The study of the genotype could be decisive for or for not to exclude the presence of a risk of invagination thus avoiding vaccination,” is not a recommendation to modify the Regional Immunization Schedule but just a proposal to implement the evidences on this subject. The presence of many recent studies, the last published on June 2016,<sup>12</sup> could be a proof of pertinence of our proposal. We clarify that in our case-report we did just supposition, so we consider and, in case, accept the possibility that it could be scientifically proven the null hypothesis is true. All this because we believe that contributing to an increase of public health in the Sicilian but also in not Sicilian population, is also our aim as that of the whole Sicilian health system.

### Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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