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Short communication

Debate on vaccines and autoimmunity: Do not attack the author, yet discuss it methodologically

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ABSTRACT

Since Jenner, vaccines and vaccinations have stirred a hot, highly polarized debate, leading to contrasting positions and feelings, ranging from acritical enthusiasm to blind denial. On the one hand, we find anti-vaccination movements which divulge and disseminate misleading information, myths, prejudices, and even frauds, with the main aim of denying that vaccination practices represent a major public health measure, being effective in controlling infectious diseases and safeguarding the wellbeing of entire communities. Recently, the authors of many vaccine safety investigations are being personally criticized rather than the actual science being methodologically assessed and critiqued. Unfortunately, this could result in making vaccine safety science a "hazardous occupation". Critiques should focus on the science and not on the authors and on the scientists that publish reasonably high-quality science suggesting a problem with a given vaccine. These scientists require adequate professional protection so there are not disincentives to publish and to carry out researches in the field. The issues for vaccine safety are not dissimilar to other areas such as medical errors and drug safety.

Since Jenner, vaccines and vaccinations have stirred hot, highly polarized debates, in which, sometimes, gut feelings, emotions and deep-rooted beliefs have prevailed over rational argumentations, leading to contrasting positions, ranging from acritical enthusiasm to blind denial [1]. On the one hand, we find anti-vaccination movements, which divulge and disseminate misleading information, myths, prejudices, and even frauds, with the main aim of denying that vaccination practices represent a major public health measure, being effective in controlling infectious diseases and safeguarding the wellbeing of entire communities [2].

On the other hand, we have a huge body of research which is mainly financed and sponsored by pharmaceutical industries and is, as such, potentially biased [3]. Public institutions like universities and research centers should have the onus to promote more independent researches and investigations. Negative findings and negative events, such as adverse effects, tend, indeed, to be under-reported and under-recognized [4,5]. A comprehensive survey carried out on randomized vaccination trials found that non-industry sponsored trials were 4.42-fold (statistically significant, with a p-value of 0.008) more likely to find and report negative or mixed results [6]. Furthermore, some vaccine manufacturers exert an overly aggressive lobbying activity, influencing (directly or indirectly) legislative drafting, policymaking, and new vaccines uptake [7]. Disclosure of potential conflict of interests, ether real or perceived, which, sometimes, authors fail to reveal, is therefore of crucial importance, not invalidating, of course, the results of scientific works *per se*, but enabling readers and other authors to make a more detached and comprehensive opinion. It is important as well to ensure a timely publication of clinical trials findings [6].

Recently, an expert opinion of a reputed Italian Cochrane reviewer, Dr. Vittorio Demicheli, of the Cochrane Acute Respiratory Infections Group, stating that the new Italian expanded immunization plan was not based on scientific evidences has raised criticism from the scientific community, which has [8,9], at least partially, focused on personal attacks and allegations rather than focusing on methodological issues [10,11].

A paper reporting adverse effects after the anti-human Papillomavirus (HPV) quadrivalent vaccine (Gardasil™) administration in an animal model, was first accepted in the journal "Vaccine" after undergoing formal peer-review and scrutiny [12], subsequently it

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was first temporarily removed and, then, withdrawn at the request of the Editor-in-chief of the journal [13]. The paper has been resubmitted to another journal for publication and was finally published [14]. Other articles [15,16] concerning the so-called "autoimmune/auto-inflammatory syndrome induced by adjuvants" (ASIA) or Shoenfeld's syndrome have been similarly "attacked" [17]. A very recent article published in the open-access journal "Scientific reports" of the Nature group by a Japanese group of immunologists and reporting the effects of HPV vaccination administered in a murine model [18] is being heavily criticized in blogs by vaccinologists and oncologists, asking for its retraction [19]. At the moment of writing/updating/revising the current article, the manuscript has not been retracted yet and it has been quoted 5 times.

Instead of focusing on methodological issues and content, the "prevailing wisdom" has put to rest any view that would contradict the sacred "doctrine" of vaccinology. Some researchers, thinking that their promotion and carrier could be jeopardized, prefer not to expose themselves [20]. A highly internationally respected British epidemiologist based in Rome (Italy), Dr. Tom Jefferson, had to face hostile reactions from colleagues and to eat alone during a meeting on influenza because of his claims on relatively low influenza vaccination effectiveness, not exactly aligned with the currently mainstream orientation of the scientific establishment [20].

From a medical standpoint, vaccines may have side effects, even though rare: this is the price to pay for the herd-immunity. It is important to discuss vaccination side-effects, in a balanced and detached way, accurately reporting their magnitude both in clinical and epidemiological terms and performing high-quality clinical studies, with adequate controls and proper sample sizes. Since studies could be statistically underpowered to capture rare events, meta-analyses, by pooling together different studies, could shed light on the strength of association between the insurgence of a side-effect and the vaccination, which should be verified from a causal point of view. While some vaccines have been discontinued/interrupted for different reasons (utilizing an obsolete technology, low demand and low sale volumes, marketing strategies, etc.), in the past, some vaccines have been withdrawn from the market because of safety concerns and potential side-effects, even though not supported by the preponderance of evidence: for example, the oral, live attenuated, tetravalent RotaShield™ vaccine (American Home Products, formerly Wyeth-Ayerst Laboratories), the first vaccine against Rotavirus infection, licensed in August 1998 and voluntarily withdrawn in October 1999 after the report of a number of cases of intussusception [21,22]. However, if some preliminary studies showing an association between rotavirus vaccination and intussusception have been criticized for failing to meet with the above-mentioned quality criteria and for not taking into account cumulative intussusception rates, or recency of wild-type rotavirus infection, some large high-quality studies have confirmed a causal relationship between intussusceptions risk and vaccine administration. The "Rotavirus Intussusception Investigation Team" collected and analyzed data from a cohort of 429 infants with intussusception and 1763 matched controls performing a case-control analysis as well as analyzed data from a sample of 432 infants with intussusception carrying out a case-series analysis. An increased risk of intussusception 3 to 14 days after the first dose of Rotavirus vaccine was found in the case-control analysis (adjusted odds ratio or aOR = 21.7 [95% confidence interval or 95%CI 9.6–48.9]), whereas, in the case-series analysis, the incidence-rate ratio was 29.4 (95%CI [16.1–53.6]). The increase in the risk of intussusception after the second dose of the vaccine was smaller [23]. Similar findings were obtained by a population-wide study [24]. On the other hand, an ecological electronic databases-based study [25] could not find any association between Rotavirus administration and intussusceptions risk, which led the authors to postulate the "trigger-compensatory decrease hypothesis" (in other words, the Rotavirus vaccine would lead to an increased number of intussusception cases in the immediate post-immunization period in a subset of infants, but it would protect against intussusception occurring after subsequent infection with wild-type Rotavirus in the long-term). There were some controversies following the publication of this study and some scholars pointed out some methodological flaws [26]. It is interesting to note that, even questioning the validity of the study, the debate focused on methodology and did not degenerate to the level of personal allegations. Observations and criticisms came mostly from Dr. Kapikian's National Institutes of Health (NIH) group [27] that had initially developed the Rhesus rotavirus vaccine initially and, then, it on to Wyeth Laboratories for clinical trial and licensure. Fortuitously, discussion was quite fair and constructive. Researchers did not attack the integrity of the Centers for Disease Control and Prevention (CDC) researchers and tried, instead, to use and rely upon scientific evidence.

Despite some nuances and criticisms – but every study is affected by some shortcomings – the risk of intussusceptions after Rotavirus vaccine administration is generally accepted as real. A similar risk has been found even with the second generation of Rotavirus vaccines, which initially did not see this risk despite larger phase 3 trials (recruiting approximately 60,000–70,000 infants). However, post-licensure studies and trials have documented an increased risk in several high- and middle-income countries, at a rate of ~1–6 excess cases per 100,000 vaccinated infants [28]. Intussusception has been, as such, included in the United States (US) Vaccine Injury Table for compensation.

This teaches us of the importance of performing different kinds of studies (cohort, case-study, case series or other investigations) and not to rely on a small number of researches, which cannot alone contribute to establish a definitive truth, but can provide some pieces which should be taken together and, if necessary, reconciled [29]. This has practical implications especially for decision- and policy-makers, who have to decide whether adopt or not the new vaccine candidate [30].

A similar story is the story of the association between swine influenza vaccine and risk for Guillain–Barré syndrome (GBS). A CDC study [31] was attacked by Doctor Leonard Kurland, a prominent neurologist at Mayo Clinic [32,33], who defined the finding of the CDC an "artifact". But Kurland ultimately joined the "Expert Neurology Group" and the study as a co-author, even when the final results (relative risk or RR = 7.1) confirmed that the original CDC study was accurate (RR = 7.6) [34].

This (together with the Rotavirus vaccines experiences) is a clear example of how disagreements in vaccine safety can and should be handled scientifically.

Another example, even though in this case of an alleged adverse effect, is given by the LYMErix™ vaccine, a vaccine against Lyme disease produced by SmithKline Beecham (now GlaxoSmithKline), expressing outer-surface protein A (OspA) of *Borrelia burgdorferi* strain ZS7 in *Escherichia coli*, with aluminum hydroxide as an adjuvant. This vaccine was approved by the US Food and Drug Administration (FDA), released in December 1998 and voluntarily withdrawn by the same manufacturer in February 2002 [35,36], following the publications of articles which stated the so-called "molecular mimicry hypothesis" and a higher risk of developing autoimmune arthritis in Human Leukocyte Antigen – antigen D Related (HLA-DR) patients [37], even if further studies did not support this claim. No statistical differences could be, indeed, detected between early or late onset arthritis in vaccinees *versus* placebo recipients. Furthermore, no elevated rates of arthritis in vaccinees could be found *versus* background rates or rates in placebo recipients [38]. In conclusion, a number of events – not based on solid scientific evidences – conspired to the withdrawal of the vaccine.

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