

## “My son can not attend the school because 5 classmates are unvaccinated”. On the question of compulsory vaccinations and the risk for immune-compromised children into the schools: the case of paediatric cancer patients

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### ABSTRACT

Since 2017, 10 vaccines are compulsory for newborns in Italy and unvaccinated children are not admitted to kindergartens. Recently the Italian Government announced the perspective of reforming the law about the compulsory vaccination. A debated started about the presence, in the same class of the schools, of unvaccinated and immunocompromised children. Cancer is the one of the most important cause of immunodepression among children: after the chemotherapy, there is a period of 13–23 months in which the cancer survivors have to come back at the school and at to the “normal life” (even for psychological exigency) but remain at risk of infectious disease for the immunodepression. The most important chance to protect this subgroup of patients remains the herd immunity.

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### Letter

Dear Editor,

Since 2017, 10 vaccines (against tetanus, diphtheria, poliomyelitis, hepatitis b, Haemophilus influenzae type B, pertussis, measles, mumps, rubella, varicella) are compulsory for newborns in Italy and unvaccinated children are not admitted to kindergartens.<sup>1</sup>

Recently, the Italian Government announced the perspective of reforming the law about the compulsory vaccinations. After the announcement of the Government, an important debated started among physicians and also citizens about the possibile decrease of vaccination coverage. If the coverage will decrease, the risk that in the same class of the school there is the presence of unvaccinated and immunocompromised children will be high. These scenario is very concerned for the possibility of contagion for these subgroup of children, at high risk of serious outcome in case of vaccine preventable diseases (VPDs).

In particular, on the first day of September, a family of Castelfranco (Veneto, Italy) announced that their son, recently treated for an important leukemia, will not able to attend the school because in the same classroom there are 5 unvaccinated children.

Cancer is the one of the most important cause of immunodepression among children and is still the second leading cause of death (following accidents) in children aged 5 to 14.<sup>2</sup> According data from Italian Cancer Register, in 2016–2010 in Italy it is possible to estimate 7000 cases of cancers among children and 4000 among adolescents.<sup>3</sup> Then in 1 of 8 of around 56.000 Italian school there is a child “cancer survivor”.

Cancers that are most common in children are acute lymphoblastic leukemia (ALL) (29%) and brain and central nervous system (CNS) tumors (26%). The 5-year relative survival

rate for all cancers combined improved from 58% during the mid-1970s to 83% during 2007 through 2013 for children and from 68% to 84% for adolescents. Pediatric cancers can be treated with a combination of therapies (surgery, radiation, chemotherapy, hematopoietic stem cell transplantation, targeted therapy or immunotherapy), chosen based on cancer type and stage.<sup>4</sup>

One of the main side effects related to the use of chemotherapy is the transient immunodeficiency that lasts for the entire treatment period up to 6–12 months after the suspension with the loss of vaccine immunity in patients who had completed vaccination program before starting chemotherapy as well as patients undergoing hematopoietic stem cell transplantation (HSCT) have antibody titers reduced.<sup>5</sup> A retrospective analysis conducted among children after allogeneic hematopoietic stem cell transplantation (allo-HSCT) showed that allogeneic hematopoietic stem cell transplantation recipients have a reduced antibody immune reconstitution due to the maturation block of B cells of IgM memory, compared to a more rapid immune reconstitution of T cell-dependent switched memory cells and in addition total body irradiation was associated with a reduced number of naive B cells at 6 months after HSCT and reduced IgM and switched memory B cells up to 2 years.<sup>6</sup>

Several studies have shown the deterrent effect of chemotherapy on the response of the acquired antibody vaccine before the start of treatment. One study found the decrease in antibody levels for diphtheria and tetanus toxoid (DT, TT, respectively) in 31 patients with ALL before and after chemotherapy: the percentage of seroprotected patients decreased from 39% to diagnosis at 17% after treatment for DT and from 81 to 33% for TT.<sup>7</sup> Another study showed the loss of pre-existing humoral immunity against measles, mumps, rubella and VZV after completion of chemotherapy, more often in children with ALL than in children with acute

myeloid leukemia (AML), solid tumors and Hodgkin's disease suggesting the need for a post-chemotherapy revaccination of child cancer survivors.<sup>8</sup>

The presence of non-protective antibody titres measured 6–12 months after the end of chemotherapy is higher for HBV (about 50% of patients), while it is lower for measles, mumps, rubella (between 20% and 40%) and diphtheria-tetanus-polio (between 10% and 30%).<sup>9</sup> However, while immunoglobulin levels return to normal within a few weeks after the end of chemotherapy, the T-cellular response against antigens such as Cytomegalovirus, Herpes Simplex Virus 1, Varicella-Zoster, Candida, Tetanus and Diphtheria recovers in a year or more after treatment; as well as transient B cells and B and T naïve lymphocytes are reformed in a short time while the recovery of B and T cells of memory may take several years.<sup>10</sup>

In a recent study the evaluation of 60 children treated for ALL suggested that seroprotection against VPDs in this population was suboptimal. In this study the serum antibody levels towards VPD were analysed after an average interval of 13 months after the end of chemotherapy. The titers of antibodies against tetanus, diphtheria, polio 3, Haemophilus influenzae type b (Hib) and mumps remained below the seroprotective thresholds in less than 50% of patients and no more than 80% were seroprotect against polio 1 and 2, measles, rubella and varicella.<sup>11</sup>

In cancer patients, during the chemotherapy treatment, vaccinations may result in a potentially sub-optimal antibody response compared to a healthy child; several studies concluded that non-viable vaccines based on toxoids, protein subunits, bacterial antigens or immunogenic proteins obtained with recombinant technology, which include vaccines against tetanus, diphtheria, pertussis, poliomyelitis, hepatitis B, influenza, Haemophilus, pneumococcus and meningococcus are not contraindicated, in principle, during chemotherapy.<sup>12</sup> The use of mitigated anti-virus vaccines for mumps, measles and rubella is usually not indicated for patients on chemotherapy because they are at higher risk for fever or vaccine vaccine disease.<sup>13</sup>

According the evidences, after the chemotherapy, there is a period of 13–23 months in which the children cancer survivors have to come back at the school and at to the “normal life” (even for psychological exigency),<sup>14</sup> but remain at risk of infectious disease for the immunodepression. In this period, the efficacy of re-vaccination is not satisfactory and children are at high risk of complications in case of infection: e.g., a 2015 outbreak of measles among paediatric haematology and oncology patients in Shanghai showed that the outcome of measles also in previously vaccinated oncology and post-HSCT paediatric patients was severe, because 20% of children involved in the outbreak died for the measles.<sup>15</sup>

The most important chance to protect this subgroup of patients is the herd immunity, that require the need of high vaccination coverage among children and adolescents.<sup>16</sup>

Governments (in particular the Italian Government, at this time) have to consider that the right of be healthy and alive for children and adolescents cancer survivors is probably more important that the (very concerned) right of not having their sons vaccinated.

### Disclosure of potential conflicts of interest

The authors have no conflicts of interest to declare.

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