

Seasonal viral influenza among persons with primary antibody immunodeficiency

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Clinical Implications

- Although contact with others diagnosed with seasonal influenza was high, the rate of flu illness was lower than expected, especially in those on immunoglobulin replacement therapy. Our survey results suggest that immunoglobulin replacement therapy may modify seasonal viral influenza illness in patients with antibody immune deficiency.

TO THE EDITOR:

It is well documented that intravenous immunoglobulin contains specific neutralizing antibodies against influenza viruses.¹⁻³ However, we do not know the effects of immunoglobulin replacement therapy on the frequency of seasonal influenza diagnosis, nor how many patients with primary immunodeficiency (PI) become ill with flu and receive the seasonal influenza vaccination.

A survey was conducted during the 2016-2017 influenza season to measure the prevalence of seasonal influenza illness and the proportion of patients with PI who received the vaccine.

A total of 11,533 email invitations were delivered to members of the Immune Deficiency Foundation database (Immune Deficiency Foundation's patient database of persons with PI) requesting participation in an unincentivized online survey. The survey was conducted during the month of May 2017. This field period was chosen to enable patients to recollect more accurately signs and symptoms of the 2016-2017 influenza season. A total of 1328 surveys were completed. Data from 1009 individuals aged 2 to 88 years with X-linked agammaglobulinemia (XLA), common variable immunodeficiency (CVID), or a diagnosis of hypogammaglobulinemia were analyzed. The survey study protocol were reviewed and approved by Schulman IRB Associates. Results were summarized and compared by diagnosis, age groupings (eg, children with PI and adults with PI), and current immunoglobulin replacement therapy usage, using chi-square tests. A *P* value of .05 or less was considered significant.

The demographic characteristics of our study population are presented in Table E1 (in this article's Online Repository at www.jaci-inpractice.org) for each of the antibody immune deficiencies. Seventy-four percent of children reported contact with others with flu; about half of the adults reported exposure or contact with others with the flu (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). More children (34%) than adults (19%) stayed home from school versus work in an effort to avoid flu illness (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org). Overall, 75% of

the patients received a seasonal influenza vaccination during the 2016-2017 influenza season (Figure 1). Persons with XLA (54%, *n* = 22) were less likely to receive a flu vaccination than were persons with CVID (76%) and hypogammaglobulinemia (69%) (Figure 1).

When asked about whether a diagnosis of flu was made either by a physician or other health care provider (between August of 2016 and May of 2017), most (83%, *n* = 840) patients reported to not be diagnosed with influenza (see Figure E3 in this article's Online Repository at www.jaci-inpractice.org), although exposure to flu was reported to be high—74% in children and 46% in adults (Figure E1). When stratified by age, children (30%) were twice as likely to be diagnosed than adults (15%). There was no difference between patients with CVID or patients with hypogammaglobulinemia; the diagnosis of flu was much less in patients with XLA (10% overall—4 of 41 patients), and 16% in children (*N* = 3), and in only 1 adult patient with XLA (*N* = 22) (Figure E3). In approximately 26% of children, the diagnosis was confirmed by nasal or throat swab; only approximately 10% of adults had their flu symptoms confirmed by laboratory test. Because this survey is self-reported, it is also possible that the “flu” illness was some other common upper respiratory tract viral illness. Very few patients with XLA received any medication for their flu; many more patients with CVID received medication, mainly Tamiflu.

Figure 2 shows the seasonal influenza diagnosis in those patients on or not receiving replacement immunoglobulin treatment. In children with XLA, only 1 of 17 children on immunoglobulin therapy developed influenza, whereas both the children with XLA not on immunoglobulin therapy developed influenza (*P* < .05). In adults with XLA, only 1 of 20 developed flu symptoms. Although there was no difference in children with CVID, only 14% of adults with CVID on immunoglobulin therapy developed flu, whereas 42% of adult patients with CVID off immunoglobulin therapy developed the flu (*P* < .001). A similar picture was seen in adults with hypogammaglobulinemia in which only 12% on immunoglobulin therapy developed the flu in contrast to 50% not receiving immunoglobulin therapy who developed the flu (*P* < .001).

Using a patient survey instrument, our aim of this study was to determine the proportion of patients with antibody immune deficiency who received a seasonal influenza vaccine, the prevalence of flu in this population during 1 viral influenza season, that is, 2016-2017, and whether replacement immunoglobulin therapy modifies the occurrence of seasonal viral influenza illness. It is well documented that intravenous immunoglobulin contains specific neutralizing antibodies against influenza viruses.¹⁻⁴ Yunoki et al³ found that immunoglobulin products even before the 2009 pandemic (1999 and 2008) contained HI and VN antibodies to the pandemic 2009 H1N1 and the classical swine H1N1 viruses. Immunoglobulin containing high-titer antibodies to the 2009 pandemic virus provided complete protection in a dose-dependent regimen against lethal pandemic H1N1 virus challenge in severe combined immunodeficiency mice.⁵ These studies suggest that significant specific and cross-reactive HI and VN antibodies are in the immunoglobulin pool that could serve to protect antibody immune-deficient patients.

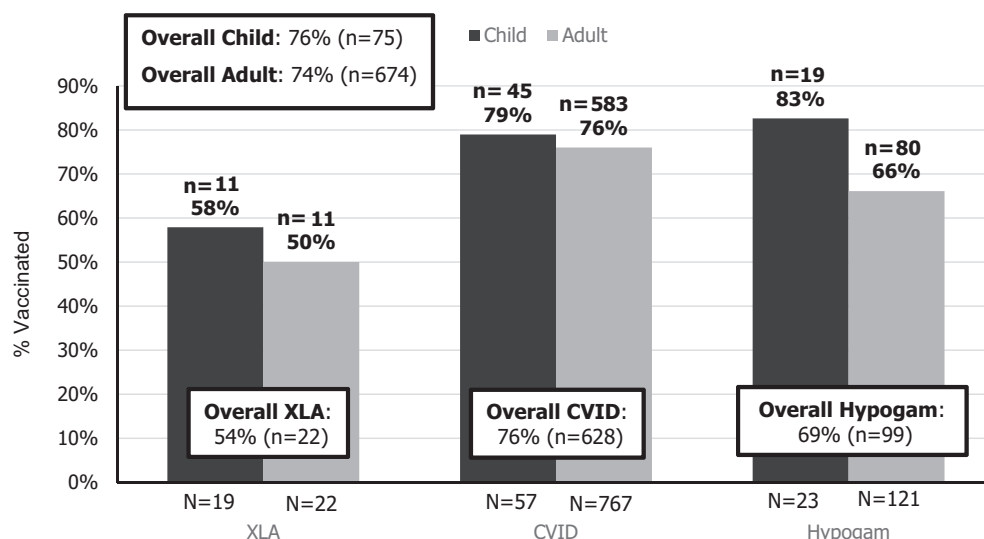


FIGURE 1. Seasonal influenza vaccination for children and adults by PI diagnosis. On the survey, the question was asked whether the child/person with PI had received a seasonal influenza vaccine at any time since August 2016 for the 2016-2017 influenza viral season. *Hypogam*, Hypogammaglobulinemia.

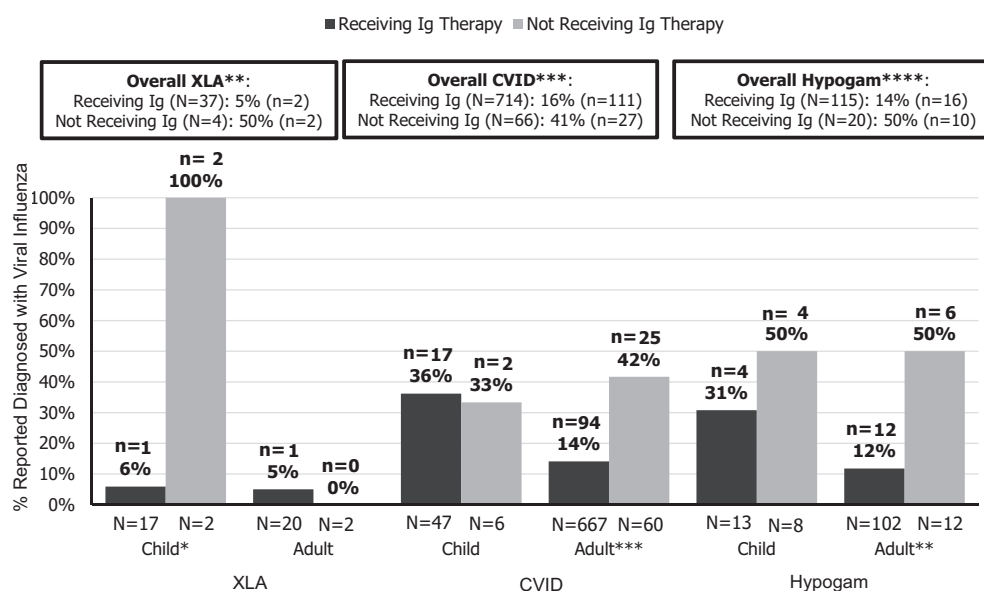


FIGURE 2. Seasonal influenza diagnosis and immunoglobulin replacement therapy for children and adults by PI diagnosis. On the survey, the question was asked whether the child/person with PI was receiving immunoglobulin replacement therapy at the time he or she developed the flu. Overall, patients receiving immunoglobulin therapy had significantly less flu diagnosis (XLA: 5% vs 50%, $P < .01$; CVID: 16% vs 41%, $P < .001$; hypogammaglobulinemia: 14% vs 50%, $P < .001$). More adults with CVID and hypogammaglobulinemia receiving immunoglobulin therapy did not develop seasonal influenza illness than those not receiving immunoglobulin therapy (adult CVID 14% vs 42%, $P < .001$; adult hypogammaglobulinemia 12% vs 50%, $P < .01$). *Ig*, Immunoglobulin; *Hypogam*, hypogammaglobulinemia.

Although reported exposure to flu was high—74% in children and 46% in adults (Figure E1)—the great majority (83%, $n = 840$) of patients were not diagnosed with influenza (Figure E3). The XLA patient group is of special interest because they cannot produce specific antibodies in response to influenza vaccination. The incidence of clinical flu in patients with XLA was only 2 of

37 patients (5%) in those patients with XLA on immunoglobulin replacement therapy. Similar trends were seen in adults with CVID and hypogammaglobulinemia. A high proportion of patients with CVID and hypogammaglobulinemia received the seasonal influenza vaccine (Figure 1). Thus, it is possible that they may have responded to the vaccine to produce some

protective antibodies. Several studies have shown that patients with CVID produce a poor specific antibody response following seasonal influenza vaccine.^{6,7}

In summary, because this study is based on a patient self-reported survey, we are not able to confirm the diagnosis of viral influenza based on physician information or laboratory confirmation. Furthermore, this report is also based on patient-reported contact and diagnosis of seasonal influenza without laboratory confirmation in many patients, a limitation of a retrospective patient self-reported survey. However, only 17% of those surveyed were diagnosed with influenza despite high rates of contact with others with flu illness. Our survey results suggest that immunoglobulin replacement therapy may have modified the clinical illness of seasonal influenza in patients with antibody immune deficiency. A prospective study with viral influenza laboratory confirmation would strengthen our observations.

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Conflicts of interest: M. Ballow has been an advisory board member for CSL Behring, Grifols, and Shire; speaker bureau participant for Shire and CSL Behring; consulting medical director for the Immune Deficiency Foundation; and member of the Data Safety Monitoring Board for CSL Behring, Prometic Biotherapeutics, Inc, Green Cross, and Glenmark Pharmaceuticals. The rest of the authors declare that they have no relevant conflicts of interest.

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ONLINE REPOSITORY

TABLE E1. Patients' demographic characteristics

Characteristic	XLA (N = 41)	CVID (N = 824)	Hypogammaglobulinemia (N = 144)
Age			
Children			
6 mo to 4 y	2% (n = 1)	0% (n = 0)	1% (n = 2)
5-12 y	32% (n = 13)	3% (n = 27)	10% (n = 14)
13-17 y	12% (n = 5)	4% (n = 30)	5% (n = 7)
Subtotal (N = 99)	46% (n = 19)	7% (n = 57)	16% (n = 23)
Adults			
18-49 y	41% (n = 17)	33% (n = 275)	24% (n = 34)
50-64 y	10% (n = 4)	37% (n = 308)	42% (n = 60)
65+	2% (n = 1)	22% (n = 184)	19% (n = 27)
Subtotal (N = 910)	54% (n = 22)	93% (n = 767)	84% (n = 121)
Median age (y)	24	55	54
Sex			
Male	100% (n = 41)	21% (n = 171)	23% (n = 33)
Female	0% (n = 0)	79% (n = 653)	77% (n = 111)
Race or ethnicity*			
White (non-Hispanic)	80% (n = 33)	92% (n = 753)	92% (n = 132)

Hypogammaglobulinemia was offered as an alternative to those patients who were not certain that their diagnosis was CVID but had low serum IgG at diagnosis.

*A few of the patients with CVID (N = 817) and hypogammaglobulinemia (N = 143) did not answer the question about race/ethnicity.

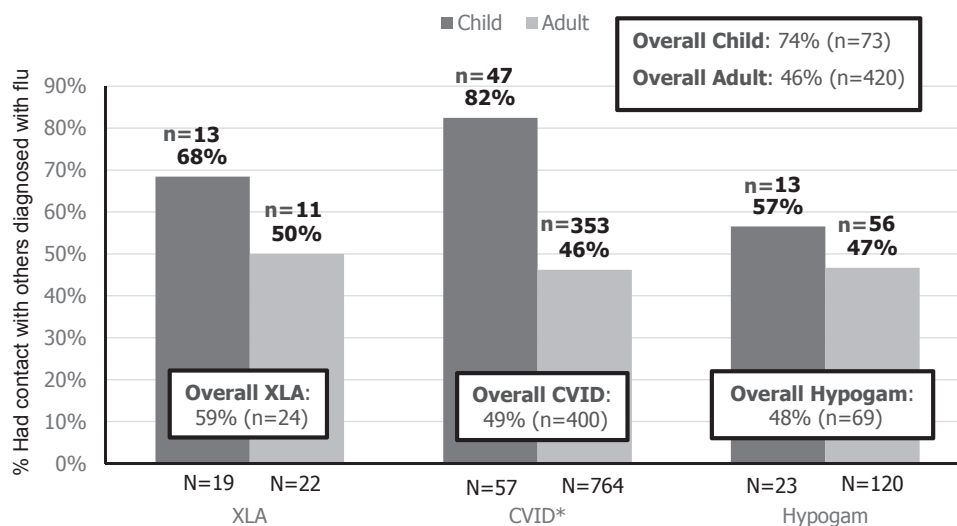


FIGURE E1. Patients who reported contact with others diagnosed with seasonal influenza for children and adults by PI diagnosis. In patients with a CVID diagnosis, children were more likely than adults to come in contact with others diagnosed with seasonal influenza infection (* $P < .001$). *Hypogam*, Hypogammaglobulinemia.

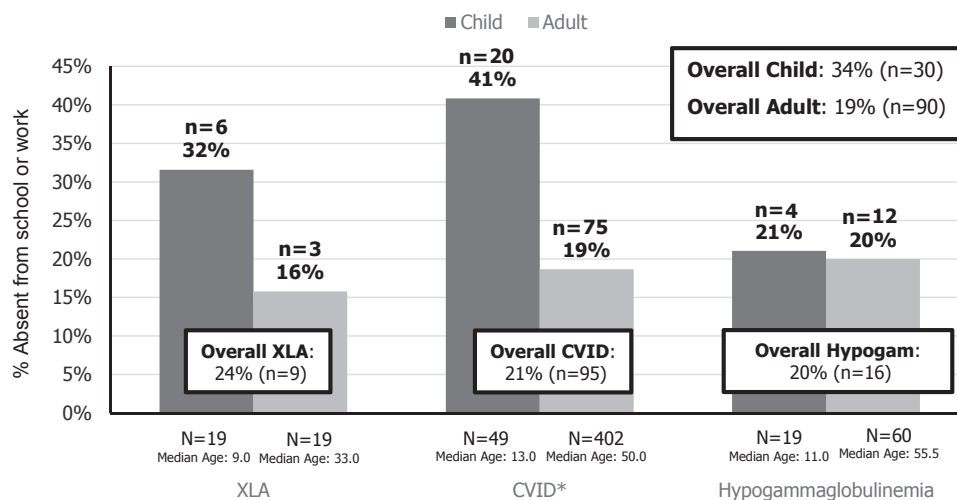


FIGURE E2. Absent from school/work to avoid seasonal influenza contact for children and adults with PI diagnosis. On the survey, the question was asked whether at any time since August 2016 was the child or person with PI removed from daycare/school or work temporarily to prevent the patient with PI from getting flu. For patients diagnosed with CVID, more children (41%) than adults (19%) were absent from school or work in an attempt to avoid contact with others with seasonal influenza illness (* $P = .001$). *Hypogam*, Hypogammaglobulinemia.

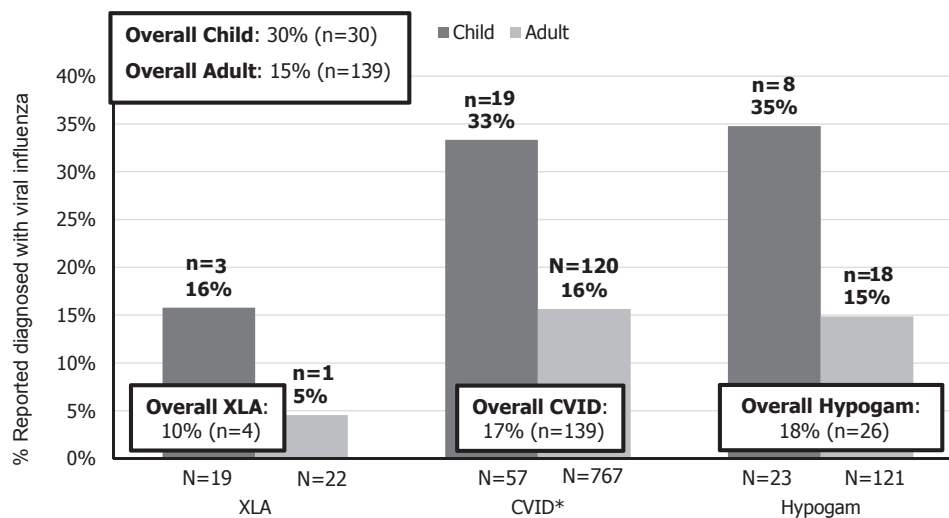


FIGURE E3. Seasonal influenza diagnosis for children and adults by PI diagnosis. On the survey, the question was asked whether the child/person with PI had been diagnosed with the flu by a physician or other health care provider since August 2016. For patients with CVID, more children than adults with CVID were diagnosed with seasonal influenza illness ($*P < .01$). *Hypogam*, Hypogammaglobulinemia.