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Ellsworth, Maine

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Dr. Meryl Nass earned her BS in Biology from MIT and her MD from the University of Mississippi in 1980, where her husband was a faculty member. She is a board-certified Internist in Maine known for expertise in anthrax, bioterrorism, anthrax vaccine and Gulf War syndrome. She identified the first modern use of anthrax as a biological weapon, which occurred in 1978 during the Rhodesian Civil War. She has testified for seven Congressional committees on bioterrorism vaccines, the anthrax letters and Gulf War syndrome. She has consulted for the Director of National Intelligence and the World Bank on the prevention and mitigation of bioterrorism. Her son practices medicine at UVM Burlington.

I want to thank the committee for holding this hearing.

My name is Meryl Nass, M.D., and I am a board certified internist practicing in Maine. I have also been involved in the study of anthrax and bioterrorism for the past 26 years.

I came late to the vaccine issue, by way of anthrax. Back in 1997, Secretary of Defense Cohen announced the US would begin vaccinating 2 ½ million soldiers for anthrax.[1] Anthrax was to be the first new bioterrorism vaccine for soldiers.

Apart from the military and VA, I have probably treated more anthrax vaccine-injured service members than anyone in the US. These service members have developed a range of disorders, which most often resemble the Gulf War syndrome/fibromyalgia/chronic fatigue syndrome pattern.

When anthrax vaccine was licensed in 1970, the federal licensing agency asked the manufacturer to conduct a human efficacy trial. But there is no evidence it was ever performed. The safety data were scant. Safety was only followed for local reactions up to 48 hours after vaccination.

Despite FDA shutting the anthrax vaccine plant in 1997, and quarantining 80% of the vaccine stockpile, the military vaccine program got underway.

Soldiers began falling ill, with seizures, syncope, and ill-defined but severe conditions that met the CDC definition of Gulf War syndrome. (In fact, Gulf War Syndrome was added as a side effect to the 2002 FDA-approved package insert for the vaccine.)

In 2004, a federal district court judge withdrew the vaccine's license. Shortly after, an Emergency Use Authorization[2] was issued enabling the defense department to continue using the now *unlicensed* vaccine. Later, FDA reissued the license, without any new studies of vaccine effectiveness or safety. The vaccine is still required for all deploying soldiers.

Why am I telling you all of this and what relevance does it have to your childcare and school vaccination policy?

Because it is a good example of when there is no prior association, odd diseases occurring in temporal relationship to vaccination are generally felt to be coincidental. The link between vaccination and diseases are only made when: large numbers are vaccinated; the disease or condition is severe; and it becomes obvious within a few weeks. And this is what happened with anthrax vaccine and Gulf War Syndrome.

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[1] US DOD, accessed at http://www.defense.gov/Releases/Release.aspx?ReleaseID=1541

[2] http://wwwnc.cdc.gov/eid/article/13/7/06-1188_article

Other examples of this include; the Rotavirus vaccine, which in 1999 caused 22 times the expected incidence of intussusception as expected;[3] the 2009-10 Swine flu vaccine that caused 9-16 times as many narcolepsy cases as expected in children in Sweden, Finland and Ireland;[4] and the 1976 swine flu debacle where 30 people died and four hundred developed Guillain Barre syndrome, an autoimmune, paralyzing disease. Much like the childhood vaccine program, manufacturers had been given a waiver of liability. The federal government commissioned a number of studies, and it was agreed the vaccine caused an increase of Guillain Barre Syndrome 8 times greater than expected in the 6-8 weeks following vaccination.

Maurice Hilleman, the dean of American vaccinologists, said he did not relax about a vaccine until it had been given to 3 million children. There is a lot of room for error when new vaccines are first marketed. In fact, the first 3 measles vaccines licensed in the US had to be junked. One caused a new syndrome, termed atypical measles; one worked poorly; and another had such severe adverse reactions it needed to be given with gamma globulin.

So each vaccine is a bit of an experiment, which is why informed consent, the right to refuse, and the ability to dialogue with one's doctor, is so critical to vaccine policy. The CDC concurs and in its Vaccine Information Statement for "Your Baby's First Vaccines" it says, "some babies should not get certain vaccines. Your doctor will help you decide."[5] Your doctor will HELP. YOU. Decide. It does not say one-size-fits-all, all the time.

In terms of immunocompromised children, they are certainly protected by the absence of some of the vaccine diseases circulating in the environment, but there are many diseases we cannot protect against, including: Epstein Barr Virus, which causes mononucleosis and certain rare cancers; and Cytomegalovirus and others such as Herpes viruses that may recrudesce from prior infections in both the immunocompromised and immunocompetent.[6]

Immunocompromised children are at considerably more risk from viruses in their own body and their local environment, than from viruses like measles.[7] The last time a child died from measles in the US was in 2003, after a bone marrow transplant. But hundreds or thousands of immunocompromised children have

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[3] Yih, et al Report June 12, 2013 http://www.mini-sentinel.org/work_products/PRISM/Mini-Sentinel_PRISM_Rotavirus-and-intussusception-Report.pdf

[4] http://www.reuters.com/article/2013/01/22/us-narcolepsy-vaccine-pandemrix-idUSBRE90L07H20130122

[5] http://www.cdc.gov/vaccines/hcp/vis/vis-statements/multi.html

[6] Lin and Liu Journal of Hematology & Oncology 2013, 6:94 http://www.jhoonline.org/content/6/1/94

[7] ibid.

died from viruses already in their bodies. The immunocompromised have been around at least as long as the philosophical exemption law has been in place, yet we don't hear about cases of immunocompromised children contracting or dying from these vaccine diseases in VT. And from the information on the VT DOH Website, the immunocompromised are not tracked in Vermont, so there are no hard numbers about how many children are really involved. The proposed law seems to be trying to fix a problem that doesn't exist.

Why is this bill, being considered now? Is Vermont facing a problem with infectious disease epidemics? My understanding is that Vermont has had only one measles case in the past ten years and in the last pertussis outbreak, close to 90% of the cases were in the vaccinated.

The Disney epidemic was declared over last Friday; no new cases were discovered for 42 days. The public health system and herd immunity worked beautifully. Not a single case of measles from the Disney outbreak has occurred in all of New England. Measles is not endemic in a single country in the entire western hemisphere.

Cases occurred mostly on the west coast. And west coast parents responded in a sensible fashion: between December and February, vaccinations to prevent measles jumped 27 percent compared with the same period last year, according to the Seattle Times. Washington parents didn't need a mandate. They reassessed the risk-benefit equation and decided accordingly.

You will hear from other physician colleagues about the need for a mandate. Yet the American Medical Association's Code of Medical Ethics preserves the right for physicians for all 3 types of vaccine exemptions, including the philosophical exemption. It seems patients and parent should be afforded the same consideration.

Diseases change, vaccines change and science changes—continually. Taking away parental choice--mandating a procedure that occasionally has lifelong, detrimental consequences--should be done very deliberately. You must be fully cognizant of the potential future, as well as immediate, ramifications—not just for the current vaccine schedule, but for all the vaccines in the future that will be added to the schedule.

Recall 2007, when Merck spent millions to convince state legislators and governors to mandate its Gardasil vaccine for preteens.[8] Is the true beneficiary of this bill the Pharmaceutical lobby, or our most vulnerable children?

Thank you for the opportunity to present this information.
Meryl Nass, MD

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[8] Washington Post, January 13, 2007 http://www.washingtonpost.com/wp-dyn/content/article/2007/01/30/AR2007013000984_pf.html

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REVIEW Open Access

Diagnosis and treatment of viral diseases in recipients of allogeneic hematopoietic stem cell transplantation

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Abstract

Viral infections are important causes of morbidity and mortality after allogeneic stem cell hematopoietic transplantation (allo-HSCT). Although most viral infections present with asymptomatic or subclinical manifestations, viruses may result in fatal complications in severe immunocompromised recipients. Reactivation of latent viruses, such as herpesviruses, is frequent during the immunosuppression that occurs with allo-HSCT. Viruses acquired from community, such as the respiratory and gastrointestinal viruses, are also important pathogens of post-transplant viral diseases. Currently, molecular diagnostic methods have replaced or supplemented traditional methods, such as viral culture and antigen detection, in diagnosis of viral infections. The utilization of polymerase chain reaction facilitates the early diagnosis. In view of lacking efficacious agents for treatment of viral diseases, prevention of viral infections is extremely valuable. Application of prophylactic strategies including preemptive therapy reduces viral infections and diseases. Adoptive cellular therapy for restoring virus-specific immunity is a promising method in the treatment of viral diseases.

Keywords: Viral infection, Allogeneic hematopoietic stem cell transplantation, Diagnosis, Treatment, Prevention

Background

Viral infections are common complications after allogeneic hematopoietic stem cell transplantation (allo-HSCT). With wide use of HLA-mismatch, unrelated and cord blood donors as alternative sources of hematopoietic stem cells, and anti-thymocyte globulin (ATG) as the standard prophylaxis of graft versus host disease (GVHD) in HLA-mismatch and unrelated donor transplantation, allo-HSCT recipients are at increasing risk for viral infections [1-5]. Fortunately, improvements in viral diagnostics, such as utilization of polymerase chain reaction (PCR)-based molecular diagnostic methods as replacement of traditional methods, facilitate the early diagnosis of viral infections [6-8]. And application of prophylactic and preemptive strategies limits the reactivation of latent viruses and development of viral diseases [9-11]. Immunotherapeutic strategies to restore virus-specific immunity, such as virus-specific cytotoxic T cells (CTL) and donor lymphocyte infusion (DLI), have been used for the treatment of viral diseases [12-14]. These developments improve outcomes of viral infections after allo-HSCT [15-17]. The aim of this article is to review the current concepts of diagnosis, prevention and treatment of viral diseases in the recipients of allo-HSCT. A brief overview will be followed by a detailed discussion on common viral diseases and viruses.

Epidemiology

In the recipients of allo-HSCT, the difference in the reported incidence is due in part to asymptomatic or subclinical manifestations in most of viral infections and the changing epidemiology of viruses as well as differences in diagnostic methods [18-23]. Till now, large-sampled epidemiological data on overall incidence of viral infections are absent in the recipients of allo-HSCT. The limited data show that community acquired respiratory viruses (CARVs) and herpesviruses are the most common pathogens [24-26]. Among the causes of CARVs respiratory tract infections, a preponderance of respiratory syncytial virus (RSV) and parainfluenza virus (PIV) are reported, followed by influenza virus and human metapneumovirus (HMPV) [19,20,27]. In herpesvirus

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family, the incidence of herpes simplex virus (HSV) and varicella zoster virus (VZV) infections as well as cytomegalovirus (CMV) diseases have significantly decreased because of the effective prophylaxis [24,25]. The reports on human herpes virus (HHV)-6 diseases are increasing in allo-HSCT recipients [28-32].

Risk factors for viral infections

In the recipients of allo-HSCT, most viral infections are opportunistic and closely related with immune status. Thus, factors influencing engraftment and immune reconstitution all potentially impact viral infections. Peripheral blood stem cell transplantation is associated with fewer viral infections than bone marrow and cord blood transplantation due to better hematopoietic and immune reconstitution [33-35]. Compared with HLA-match related transplantation, HLA-mismatch related and unrelated transplantation have an increasing risk of viral infections because immune reconstitution is delayed by the intensified GVHD prophylactic strategy, such as the use of ATG [18,36-38]. GVHD may delay immune reconstitution and is considered an independent risk factor of viral infections [36]. In addition, other factors, such as the serologic status of donors and recipients before transplantation as well as the age of recipients, may also affect the incidence of viral infections. For example, CMV-seronegative recipients receiving graft from CMV-seropositive donors are at high risk of CMV diseases [24]. Children are high-risk population of CARVs infections [26].

Diagnostic strategies

Generally, the diagnosis of viral diseases in immunocompetent individuals is based on clinical manifestations and laboratory examination. A definitive diagnosis requires detection of specific virus in specimens obtained from involved tissues and secretions as well as blood, or even histopathologic evidences. However, such a definitive diagnosis is frequently unnecessary or unavailable due to the risk associated with the invasive procedure (e.g. infection, bleeding) [25,39]. Thus, stratified diagnosis of viral infections and diseases based on diagnostic evidences is recommended [25,39]. The clinical manifestations of viral diseases in immunocompromised individuals, including transplant recipients may be different with the immunocompetent population [40]. For instance, fever does not always occur and the disseminated diseases are more common [24,25,39]. Meanwhile, viral diseases generally occur with or subsequently to other transplant complications such as bacterial and fungal infections [24,25]. For example, CMV gastrointestinal disease is particularly difficult to diagnose because it frequently presents together with gut GVHD, and diarrhea is the same symptom of these two transplant complications [24]. Therefore, in the recipients of allo-HSCT, the diagnosis of viral diseases mainly depends on laboratory examination.

Laboratory diagnostic methods mainly include viral culture, serologic testing, antigen and nucleic acid detection [6]. Table 1 showed the common methods used in diagnosis of viral infections. The golden standard for diagnosis of most viral diseases is finding of specific histopathological features and detection of virus in the involved tissues. However, biopsy is often infeasible in allo-HSCT recipients, considering that most viral diseases occur at the early stages of transplantation with concomitant thrombocytopenia or unstable vital sign. Viral culture is unsuitable in the early diagnosis because it routinely takes days to weeks and requires specific cell lines [41]. Serologic testing requires finding of progressive increasing in antibody to identify a recent infection. Unfortunately, transplant recipients are usually unable to mount sufficient antibody because of immunosuppression. Therefore, serology is less helpful for clinical decision in the recipients of allo-HSCT [24-26]. Techniques of antigen detection, including fluorescent antibody assays and enzyme immunoassays, are rapid diagnostic methods of which results can be available within hours. But the limitation of these methods is poor sensitivity compared with molecular techniques [26,42,43]. Application of PCR technique in the detection of viral nucleic acid rapidly develops the viral diagnostics [6]. In theory, any virus can potentially be detected by PCR. Now, real-time quantitative PCR (RQ-PCR) is replacing traditional gel-based PCR because it can reflect the changes of viral loads [7,44-47]. The availability of these modern diagnostic tools facilitates early diagnosis and timely intervention of viral infections. Currently, the diagnosis of viral infections in the recipients of allo-HSCT mainly relies on PCR-based methods. To investigate new or uncommon pathogens, electron microscopy or viral culture can be used. Although biopsy has the aforementioned problems and risk, it is still required in the diagnosis of some specific viral diseases, such as EBV-associated post-transplant lymphoproliferative disorder (PTLD) [25,48].

Treatment strategies

Although multiple strategies have been used [17,24-26,39], the treatment of viral diseases remains rather a challenge because few agents are available and efficacious. In the recipients of allo-HSCT, immunotherapeutic strategies to restore virus-specific immunity, such as reducing immunosuppressants, DLI and *ex vivo* generation of virus-specific CTL, are now advocated in the treatment of viral diseases [14,25,49]. However, reducing immunosuppressants is unfeasible in many patients due to potential risk of GVHD [24,25], and DLI is limited by unavailable stem

Table 1 Common methods used in diagnosis of viral infections after transplantation

Methods	Sensitivity *	Specificity#	Time§	Virus	Comments
Culture	+++	++++	+	HSV, CMV, VZV, Influenza virus, RSV, PIV, adenovirus	Gold standard
					May take weeks before results return
Shell vial culture	++	+++	++	HSV, CMV, VZV, Influenza virus, RSV, PIV, adenovirus	Reduce the testing time compared with culture
Antigen detection	++	++++	++++	Most CARVs, herpesviruses, adenovirus	Quick results
					Poor sensitivity
PCR	++++	+++	+++	All are possible	Quick results
					High sensitivity
Histopathology and immunohistochemistry	NA	NA	NA	All are possible	Detect viruses in tissue
Electron microscopy	++	NA	++++	All are possible	Require facility and experienced staff
Serology	NA	NA	NA	NA	Less helpful in diagnosis

* "+" –"++++" indicated low sensitivity to high sensitivity; # "+" –"++++" indicated low specificity to high specificity; § "+" –"++++" indicated long testing time to short testing time. NA indicated not applicable.

cell donors and the risk of exacerbating GVHD [49]. Of note, these adoptive cellular therapies are only proven efficacious for a few viruses, such as CMV, EBV and adenovirus [12,50,51]. Early intervention has a dramatic influence upon survival and may reduce the extent of permanent injury in survivors [20,52,53]. For example, in patients with CARVs infections, treatment is more effective if started prior to development of lower respiratory tract infection (LRTI) or respiratory failure [26,54,55]. Our data showed that the patients with EBV fever without tissue involvement had better treatment response than those with end-organ diseases or PTLD [4].

Prophylaxis strategies

Since specific therapy is limited to only several antiviral agents, prevention of viral infections is crucial to reduce the incidence and mortality of viral diseases. According to the different periods of transplantation, the strategies might be divided to prophylaxis pre-transplantation, during transplantation and post-transplantation. Before transplantation, selection of virus-seronegative stem cell donors for seronegative recipients, and decreasing virus loads in virus-seropositive donors and recipients should be considered. During transplantation, the strategies of conditioning and GVHD prophylaxis should be chosen prudently to minimize the delay of immune reconstitution. After transplantation, prophylaxis should be performed throughout the risk period such as pre-engraftment and GVHD. The incidence of HSV and VZV infections has decreased from 80% to lower than 5% in the recipients of allo-HSCT receiving antiviral prophylaxis throughout the risk period [25,56]. Preemptive therapy for reactivation of some latent viruses, such as CMV and EBV has been demonstrated to reduce the progression of viral diseases [24,25]. Vaccination, such as Measles–Mumps–Rubella and VZV vaccine, seems useful to prevent corresponding viral infections [57,58]. Influenza virus vaccine is suggested to be given to the recipients prior to each influenza season [59].

Viral diseases after HSCT

Respiratory diseases

Respiratory diseases after HSCT are mainly caused by CARVs [60,61]. Other viruses, such as herpesviruses and adenovirus, may also result in respiratory infections [61,62]. Majority of the patients present with upper respiratory infection, and 18-44% of these patients may progress to lower respiratory infection with mortality of 23-50% [18-21,23,63]. The incidence of respiratory diseases after allo-HSCT ranges from 3.5% to 29% [20,64], and the incidence of viral pneumonia is 2.1-14% [4,20,64-66]. Typical clinical manifestations include fever, cough, myalgias. Dyspnea is an important symptom of viral pneumonia. Some of CARVs infections show a pronounced seasonality. For example, RSV and influenza virus reach a peak incidence during the winter and spring [19]. CARVs may also result in epidemic outbreak in the wards. Herpesvirus pneumonia is usually caused by reactivation of latent viruses which occurs in severe immunosuppression such as early period of transplantation and GVHD [2,67,68].

Encephalitis /meningitis

In immunocompetent individuals, herpesviruses are the most frequent pathogens in sporadic viral encephalitis/meningitis. A retrospective study from Schmidt-Hieber et al. showed that viral encephalitis was mainly caused by human herpes virus (HHV) -6, followed by EBV, HSV, JC virus, CMV, VZV in the recipients of allo-HSCT [69]. Our data showed that herpesvirus-associated encephalitis was mainly caused by EBV followed by HSV, CMV and

VZV [70]. Recently, encephalitis caused by adenovirus is increasing [69]. The incidence of viral encephalitis after allo-HSCT was 1.2% in a retrospective study [69]. Our results revealed that the incidence of herpesviruses-associated encephalitis/meningitis was 6.3% [70]. In the recipients of allo-HSCT, viral encephalitis/meningitis usually occurs within 100 days post-transplantation. Clinical manifestations of viral encephalitis/meningitis are diverse, including fever, changes of consciousness, seizures, palsy of brain nerves and psychiatric disorders; but meningeal irritation is not common compared with healthy population [69]. The mortality of viral encephalitis/meningitis ranges from 0% to 80%, depending on virus types and timing of diagnosis and treatment [69,71].

Gastroenteritis

Rotavirus and norovirus are considered main causes of viral gastroenteritis. Currently, adenovirus and CMV are increasingly recognized as important pathogens of viral gastroenteritis in the recipients of allo-HSCT. Astrovirus-associated gastroenteritis which usually occurs in children is rarely observed in the recipients of allo-HSCT [72]. Few data are available on the incidence of viral gastroenteritis after allo-HSCT. Van Kraaij et al. documented that 19% of HSCT recipients (including allo- and auto-HSCT) developed viral gastroenteritis [73]. Fortunately, the mortality caused by rotavirus and norovirus-related gastroenteritis is rare [74-77]. The most common clinical manifestation of viral gastroenteritis is diarrhea, followed by vomiting and nausea. Rotavirus and norovirus infections are seasonal with a peak incidence in winter. Most of the patients acquire the viruses from community [74,77]. The median onset time of adenovirus and CMV gastroenteritis are 60–90 days after transplantation, and usually associated with acute GVHD [76,78].

Hepatitis

Viral hepatitis is the third cause of hepatic impairment in the recipients of allo-HSCT, and usually occurs in 3–6 months after transplantation [79]. The most frequent pathogens of viral hepatitis are hepatitis B virus (HBV) and hepatitis C virus (HCV) [80,81]. Besides, other viruses such as CMV and HSV may also result in hepatitis [24,25]. Hepatitis B and C can be caused by either virus reactivation or blood transmission. Since the carriage rates of HBV and HCV vary in different regions, the incidence of viral hepatitis varies [81,82]. Increasing virus loads in blood is valuable for diagnosis. Of note, the diagnosis of viral hepatitis should be based on exclusion of other transplant complications (e.g., sinusoidal obstruction syndrome [SOS] and GVHD). Attributed to effective prophylaxis and antiviral treatment, the mortality of hepatitis B and C is low [81,83].

Cystitis

Post-transplant cystitis usually present with hemorrhagic cystitis (HC). According to onset time, HC is divided into early-onset HC (within 48 hours of conditioning) and late-onset HC (occurring after 48 hours). Early-onset HC is often due to the toxicity of conditioning regimen such as cyclophosphamide. It is reported that 11.6-42% of patients develop late-onset HC after transplantation [84,85]. Late-onset HC was considered to be related with reactivation of latent BK virus (BKV), but this association remains controversial [86,87]. Some studies suggested that acute GVHD might increase the risk of HC [87,88]. Recently, adenovirus and CMV were suggested to be associated with late-onset HC [88,89].

PTLD

PTLD is a life-threatening complication following allo-HSCT. Approximately 90% of PTLD result from EBV-driven B cell proliferation poorly controlled by a weakened immune response. Recent data implicated that CMV and HHV-6 might contribute to the development of PTLD [90,91]. The incidence of PTLD varies from 0.5% to 22%, depending on the number of risk factors [3,68,92-94]. In the recipients of allo-HSCT, most of PTLD occur within 1 year post-transplantation, reaching a peak incidence within 3 months [95-97]. Isolated nodal involvement is the most common presentation. About 20% of patients present with extranodal involvement, and isolated extranodal involvement is not rare [93,96,98-100]. Clinical presentations of PTLD depend on location and the degree of organ involvement. PTLD with extranodal involvement usually have poor outcome. The mortality of PTLD is 50-64% [68,94]. Delay of diagnosis and treatment is associated with a high mortality (>90%) [96,101].

Other viral diseases

Bone marrow suppression is common in the recipients of allo-HSCT. Graft failure is a fatal complication after transplantation. Several viruses, such as CMV, EBV, HHV-6 and adenovirus have been recognized the causes of bone marrow suppression and graft failure [24,25,39,102]. The diagnosis of virus-associated graft failure should be based on pancytopenia, bone marrow hypoplasia, detection of virus together with exclusion of GVHD, rejection and relapse [102] .

Common viruses in allo-HSCT recipients

Herpesviruses

The known herpesviruses resulting in human diseases include α- (HSV and VZV), β- (CMV, HHV-6,-7) and γ-herpesviruses (EBV and HHV-8). Herpesvirus infections are usually asymptomatic or subclinical in immunocompetent population. The virus becomes latent in infected cells after primary infection. When immune system is

disordered or deficient, latent viruses may reactivate and result in symptomatic infections, even fatal complications [24,25]. The diagnostic methods of herpesvirus infections were summarized in Table 2.

HSV

Up to 80% of the healthy population have history of HSV-1 and –2 infections [25]. HSV-1 infection is more common than HSV-2. After primary infection, the virus becomes latent in the neuronal cells. Historically, 80% of HSV-seropositive patient developed reactivation after allo-HSCT without antiviral prophylaxis [104]. Fortunately, the incidence of HSV reactivation has now decreased to 0-3% because of prophylactic acyclovir [56,105]. HSV causes a spectrum of diseases, such as herpes, oesophagitis, bone marrow suppression, respiratory tract diseases, hepatitis and encephalitis in the recipients of allo-HSCT [25]. Due to the high rate of HSV reactivation, prophylactic oral acyclovir has been administered routinely in allo-HSCT recipients. Intravenous acyclovir should be considered for patients with poor drug absorption [17,106]. Valacyclovir is an alternative prophylactic agent with good bioavailability [107-109]. Acyclovir is recommended as the therapy for severe mucocutaneous or visceral HSV disease in transplant recipients [25]. Valaciclovir and famciclovir are considered as alternatives for less serious manifestations of HSV diseases [25]. The recommended drug for acyclovir-resistant HSV is foscarnet [17]. Cidofovir might be effective to treat HSV infection which is resistant to both acyclovir and foscarnet [110].

VZV

Varicella caused by primary VZV infection is a common childhood disease. After primary infection, VZV establishes latency in the dorsal root ganglia in immunocompetent host. The reactivation of VZV results in herpes zoster [111,112]. In the recipients of allo-HSCT, VZV is also an important cause of viral encephalitis. VZV immunization is advocated in recipients without a history of varicella. Varicella vaccine has been showed to be safe in children with leukemia, but few data are available in transplant recipients [106]. Besides, vaccination of VZV-seronegative individuals who may be in contact with the patients during transplantation should be done [25]. Zoster immune globulin (ZIG) and varicella-zoster immune globulin (VZIG) are passive antibody prophylaxis in seronegative recipients after exposure to varicella [113]. Acyclovir and valacyclovir prophylaxis were proven effective in several trials [9,114-117]. Antiviral therapy with acyclovir is recommended in the treatment of VZV infection [25]. Acyclovir has been shown to reduce the progression and dissemination of VZV infection [118,119]. Treatment with brivudin or famiciclovir is effective in immunocompromised population [120,121]. Foscarnet and cidofovir are alternative agents against acyclovir-resistant VZV infection [122].

Table 2 Laboratory diagnosis of herpesviruses

Viruses	Methods
HSV	PCR(preferred); antigen detection [25]
VZV	PCR(preferred); Immunofluorescent-antibody staining [25]
CMV	PCR(preferred); CMV antigen (pp65) detection [24,103]
EBV	PCR; immunohistochemistry or in situ hybridization to detect EBV in biopsy specimens [25]
HHV6-8	PCR [24]

CMV

CMV infects 70-80% of the healthy individuals and establishes latency in peripheral blood monocytes and tissue macrophages. Till now, CMV remains one of the most important viruses and causes of death in the recipients of allo-HSCT. CMV-associated end-organ diseases include pneumonia, enteritis, hepatitis, retinitis and encephalitis, and so on; CMV syndrome is defined as CMV-associated fever without sign of CMV end-organ disease [24]. Majority of CMV infections are caused by reactivation of virus which usually occurs within 3 months post-transplantation [8,24,78]. Approximately 75% of CMV-seropositive recipients develop CMV reactivation, and 20-30% of these patients develop CMV disease without intervention [17,24]. Preemptive therapy based on CMV antigenemia or DNA-emia significantly reduces the development of CMV disease in allo-HSCT patients [24,123]. However, the mortality of CMV disease is more than 50% even with treatments [67,124]. The diagnosis of CMV infection includes CMV viremia, CMV syndrome and CMV end-organ disease [24]. Historically, CMV antigen (pp65) detection was widely used in diagnosis of CMV infection. Recently, PCR is replacing antigenemia assay to be the preferred diagnostic method due to higher sensitivity [24,103].

Preemptive therapy based on CMV viremia has become the standard prevention of CMV diseases after transplantation [24]. The first-line preemptive therapy is ganciclovir with a minimum duration of 2 weeks depending on whether CMV is detected at the end of the course [24,125,126]. The main side effect of ganciclovir is bone marrow suppression which results in the increase of bacterial and fungal infection [127,128]. Valganciclovir is an alternative with good bioavailability [129-131]. Foscarnet and cidofovir are the second-line prophylactic agents considering of drug-associated toxicity [24].

Ganciclovir is the first-line treatment of CMV diseases. The recommended therapy of CMV pneumonia is a

combination of intravenous ganciclovir and high dose immune globulin [24,124,132]. In view of toxicity and effective rate, cidofovir and foscarnet are used as second-line therapy of CMV diseases [24]. Ganciclovir resistance is uncommon and usually mediated through mutations in the UL97 gene. Cidofovir is used in the treatment of CMV disease which is resistant to ganciclovir and foscarnet, with an effective rate of 50% [133]. Since it has been known that specific immune response to CMV is important to control reactivation, CMV-specific CTL has been used in prophylaxis and treatment of CMV viremia in several studies [50,51,134]. Leen et al. reported that the response rate of CMV-specific CTL was 73.9% in the treatment of CMV diseases after allo-HSCT [50].

EBV

Approximately 90% of healthy adults have been infected by EBV. After primary infection, EBV is latent in B cells (6, 8). Primary EBV infection or reactivation usually induces asymptomatic infection or infectious mononucleosis in immunocompetent people. However, EBV results in a spectrum of diseases in the recipients of allo-HSCT, ranging from fever, end-organ disease (pneumonia, encephalitis/myelitis, and hepatitis) to PTLD [4]. Among these diseases, PTLD is most common [4,25]. Our data showed that the 3-year cumulative incidence of EBV disease were 15.6% in the recipients of allo-HSCT, with the PTLD incidence of 9.9% [4]. EBV disease is usually caused by reactivation of latent virus after allo-HSCT. After transplantation, 14-65% of recipients developed EBV reactivation, depending on different risk factors that the recipients have [37,68,135]. The diagnosis of EBV infection includes EBV viremia, probable end-organ disease and proven end-organ disease as well as PTLD [25].

Since rapid increase of EBV-DNA loads in blood is considered to be related with subsequent EBV diseases [136], routine monitoring of EBV viral loads is necessary after transplantation [25]. Preemptive therapy based on EBV-DNA loads in blood and risk factors for EBV disease has yielded good results [25]. Preemptive therapy is now developing mainly in two directions: adoptive cellular therapy (EBV-specific CTL) and B-cell depletion with monoclonal antibodies. EBV-specific CTL has been demonstrated effective to prevent EBV disease in several studies [135,137], but the production of CTL requires time. Besides, reduction of immunosuppressants is an ideal preemptive therapy, but frequently not available due to the risk of GVHD. Rituximab is easily available and has shown little toxicity [138]. Based on the above, rituximab is recommended as the preferred preemptive therapy, followed by reduction of immunosuppresants and EBV-specific CTL in the European guidelines [25].

The therapeutic strategies of EBV disease include antivirus, restoration of T cell response and clearance of the EBV infected cells. Antiviral agents (e.g. acyclovir and ganciclovir) can reduce EBV replication, but is not active in PTLD presumably because that viral thymidine kinase expression is low during lytic phase and lack during latency [139,140]. Recently, a novel agent arginine butyrate, which induces EBV thymidine kinase transcription, has been shown *in vitro* to render latently infected EBV-immortalized B cells susceptible to ganciclovir [139,140]. Treatments to restore T-cell reactivity include reduction of immunosuppressants and adoptive cellular therapy (CTL and DLI) [25]. Anti-CD20 monoclonal antibody (rituximab) is used to clear EBV-infected B cells [25].

According to the European guidelines, rituximab is a recommendation of highest priority for treatment of PTLD; other first-line treatment includes reducing immunosuppressants, EBV-CTL and DLI [25]. Chemotherapy is recommended as the second-line therapy [25]. The response rate of rituximab monotherapy was reported 44-69% whereas the relapse rate was 18-32% [141-144]. Compared with rituximab, adoptive cellular immunotherapy has higher response rate (50-88%) and fewer relapse (0%) [12,145,146]. Nevertheless, the utilization of adoptive cellular therapy is limited by the aforementioned disadvantages such as time and facilities required by CTL production as well as potential risk of GVHD caused by DLI [12,14,97,137,145]. Chemotherapy is reported to induce remissions in 40-50% of the PTLD patients but with significant treatment-related mortality and relapse rate [141,147]. Therefore, in the 'era of rituximab', chemotherapy is barely used unless for CD20-negative PTLD or combination with rituximab [145]. To date, there are no randomized trials to compare the efficacy between rituximab alone and rituximab combined with chemotherapy. Trappe et al. [148] suggested that sequential first-line treatment with rituximab followed by chemotherapy is more efficacious than first-line rituximab monotherapy followed by chemotherapy at progression or relapse. In our study, we introduced a sequential therapeutic strategy that is rituximab-based treatments followed by adoptive cellular immunotherapy. The results revealed that this strategy might elevate response rate and decrease the relapse rate. Besides, this strategy might overcome the drawback of long time frame to product EBV-CTL and reduce the risk of GVHD caused by DLI. It remains a matter of discussion that whether histology subtypes of PTLD affect the outcome of rituximab-based treatments [148,149]. The prognosis of PTLD with extranodal or multi-organ involvement is dismal compared with isolated nodal involvement [34,150]. Some studies suggested that intrathecal rituximab is efficacious against PTLD with CNS involvement [151-153]. Other therapeutic options include local radiotherapy and operation, which is mainly for the patients with significant compression symptoms [145].

Clinical data on EBV fever and end-organ diseases are quite limited. Rituximab seems efficacious to treat EBV fever, with a response rate of 100% [4,154]. The treatment strategies of EBV end-organ diseases are similar with PTLD. However, the efficacy of rituximab monotherapy in patients with end-organ diseases seemed poorer than those with PTLD [4].

HHV6-8

Approximately 50% of recipients develop HHV-6 reactivation after transplantation [28,30]. HHV-6 diseases include encephalitis, interstitial lung disease and delayed engraftment [24,31]. Two small-sampled studies suggested that ganciclovir might be effective to prevent HHV-6 reactivation in allo-HSCT recipients [155,156]. However, no widely accepted prophylactic strategy is recommended considering of the drug toxicity and the low incidence of HHV-6 diseases [24]. Both ganciclovir and foscarnet were reported to be effective against HHV-6 diseases [157].

HHV-7 infection/reactivation is infrequent in the recipients of allo-HSCT, and little information about HHV-7 diseases is available. Therefore, prophylaxis and treatment of HHV-7 infection remain unclear [24].

HHV-8 is recognized the cause of Kaposi's sarcoma in human immunodeficiency virus (HIV) infected patients [158]. HHV-8 infection is rare in the recipients of allo-HSCT, and usually results in non-malignant diseases such as hepatitis, bone marrow suppression [159,160]. Currently, clinical data on prevention and treatment of HHV-8 diseases after allo-HSCT are based on case reports. Cessation of immunosuppressants and foscarnet were used for treatment, and the efficacy requires further study [161,162].

CARVs

CARVs, including orthymyxo- (influenza virus), paramyxo- (RSV, PIV, HMPV), picorna- (human rhinovirus [HRhV]), coronaviruses (HCoVs), human bocavirus (HBoV), and polyomaviruses, are important pathogens of respiratory tract infections in the recipients of allo-HSCT, [26]. Significant overlap in clinical manifestations is observed in CARVs infections, and atypical presentations are common. Table 3 summarized the diagnostic methods and epidemiology of CARVs infections in the recipients of HSCT. Antigen detection has a good specificity and a short turn-around time of several hours, but a lower sensitivity compared with PCR [59]. Currently, PCR for detection of virus nucleic acid is preferred in diagnosis [26].

Infection control is the mainstay of prevention against CARVs disease. Healthcare facilities and infection control measures, including isolation and strict protection measures for healthcare workers and contacts, should be applied to HSCT recipient [26,168]. Besides, recipients and contacts should adhere to good personal hygiene. Recipients should avoid contact with individuals with CARVs respiratory infections in the hospital and the community [26,168].

RSV

RSV is one of the most common respiratory pathogens in most series including HSCT recipients. Limited data are available on prevention of RSV infection. In some studies, treating upper respiratory tract disease was effective to reduce the progression to pneumonia and improve the outcome [26,163,164]. But some other reports did not confirm this result [169,170]. Aerosolized ribavirin with or without RSV-specific immunoglobulin or intravenous immunoglobulin has been used to treat RSV pneumonia, with the 30-days survival of approximately 60% [19,54,64,163,171]. Treatment started before respiratory failure is associated with improved outcome [19,54,64]. Intravenous ribavirin is less effective but increases the side effects [55]. The efficacy of palivizumab (an RSV-specific monoclonal antibody) in HSCT recipients is not well defined [172,173].

PIV

PIV infection occurs throughout the year, with the highest incidence in July and September [166]. The prophylactic and therapeutic strategies against PIV infection remain a matter of discussion. A large-sampled retrospective analysis suggested that aerosolized ribavirin with or without intravenous immunoglobulin did not improve the outcome of PIV pneumonia [165]. Elizaga et al. documented that the effective rate of aerosolized ribavirin therapy was 100% in the treatment of upper tract infections, whereas only 25% of patients with PIV pneumonia survived [166].

Influenza virus

To prevent influenza after transplantation, the European guidelines recommended that vaccination should be performed in HSCT recipients with seasonal influenza vaccine [59]. Meanwhile, vaccination of healthcare workers and close contacts with HSCT recipients is advocated [59]. Prophylaxis with oseltamivir seems useful after exposure and during the period of influenza circulation [59,174]. M2 inhibitors, amantadine and rimantidine have no longer been used for treatment due to widespread resistance [175,176]. Neuraminidase inhibitors (oral oseltamivir or inhalational zanamivir) are now the most widely used therapeutic agents for influenza, with an effective rate of 46-100% [21,177,178]. Intervention initiated within 48 hours of symptom onset was associated with reduced risk both for pneumonia and the need for intensive care [21,179].

Other CARVs

At present, respiratory infections after HSCT caused by HCoV, HMPV and HRhV have been increasingly

Table 3 CARVs infections after HSCT

Viruses	Diagnostic methods	Incidence of infection	Progression to LRTI	Mortality with LRTI
RSV	PCR(preferred); Antigen detection; culture	2.2-5.8% [27,64,163]	17-84% [19,164]	7-83% [19,164]
PIV	PCR(preferred); Antigen detection; culture	Up to 17.9% [19,165]	50%[19,165]	Up to 75% [166]
Influenza virus	PCR(preferred); Antigen detection; culture	1.7-9.0% [19,21,23]	18-44% [19,21,23]	5-37% [19,21,23]
HMPV	PCR(preferred); Antigen detection;	2.5-9% [26]	21-40%	33-40%
HRhV	PCR(preferred); culture	22.3% [26]	<10% [26]	?
HCoV	PCR	11% [167]	?	?
HBoV	PCR	2.1%[167]	?	?

?, absence of significant studies.

recognized. In our recent study, HCoV was found in 16.2% of the recipients within 6 months after HSCT, including 12% of LRTI; HMPV and HRhV was found in 5.4% and 2.7% of the recipients, respectively. The efficacious prevention and treatment of HMPV infections have not been well described. Ribavirin and/or intravenous immunogloblin were used to treat HMPV pneumonia in several studies but the efficacy was not defined [26,180]. The prevention and treatment strategies of HRhV are limited by the lack of antiviral agents and clinical trials. There are no recommendations on prophylaxis and treatment due to absence of effective antiviral agents and appropriate clinical studies [26].

Adenovirus

Adenovirus is increasingly recognized as an important pathogen in immunocompromised individuals, especially in the recipients of allo-HSCT. Adenovirus infection may arise from either reactivation of latent virus or acquisition from community. Contrary to self-limited infection in most immunocompetent individuals, adenovirus causes lethal end-organ or systemic diseases in immunocompromised patients [39]. The incidence of adenovirus infection ranges from 0-6% in adult allo-HSCT recipients, and half of these patients developed adenovirus-associated diseases [18,22]. Adenovirus diseases include respiratory tract disease, gastroenteritis, encephalitis, myocarditis, nephritis and multiple organ involvement [18,22]. The mortality was reported as high as 100% in adenovirus pneumonia [39] and 61% in disseminated disease [181]. Now, PCR is the standard diagnostic method of adenovirus infection [39]. Other diagnostic approaches include viral culture and antigen detection [39].

Strict isolation and hygiene measures are advocated in patients shedding the adenovirus to prevent horizontal transmission and nosocomial outbreaks. Bordigoni et al. [182] suggested cidofovir or DLI seemed encouraging approaches to prevent adenovirus diseases, whereas ribavirin and vidarabin were ineffective.

The efficacy of ribavirin is controversial in the treatment of adenovirus diseases [182-184]. Several studies documented that cidofovir was efficacious against adenovirus [75,76,182,185]. Considering of the insufficient immune response to control adenovirus reactivation in the patients, adenovirus-specific CTL seems a promising therapy [186,187]. Leen et al. reported that the effective rate of adenovirus-specific CTL was 77.8% in the recipients of allo-HSCT [50]. In addition, reduction of immunosuppressants is recommended for prophylaxis and treatment if possible [18].

Gastroenteritis viruses

Rotavirus and norovirus are important pathogens of viral gastroenteritis. The incidence of rotavirus infection is 6.7-11.5% in HSCT recipients, and death is rare [73,74]. Antigen detection as well as PCR is used in diagnosis of rotavirus infection. At present, norovirus as a cause of gastroenteritis after allo-HSCT is not well recognized [188]. In pediatric HSCT recipients, the incidence of norovirus-associated gastroenteritis was reported 12.9% and no norovirus-associated mortality was observed [77]. Detection of norovirus RNA by PCR is the main diagnostic evidence. Till now, little information is available about prevention and treatment of rotavirus and norovirus in the HSCT population. Oral immunoglobulin and nitazoxanide have been used in some studies [74].

Hepatitis viruses

Among hepatitis viruses, HBV and HCV are important causes of hepatic impairment in the recipients of allo-HSCT. Hepatitis virus-positive donor should be avoided if alternatives exist.

For HBV-negative recipients, pre-transplant vaccination and HBV-specific immune globulin should be considered if the donors are HBV surface antigen positive. For HBV-positive recipients, administration of antiviral agents (i.e. lamivudine, famciclovir, Entecavir and adefovir) pre- and post-transplantation is advocated to reduce HBV replication [189,190].

Administration of ribavirin and interferon should be considered to decrease or clear the viral loads before transplantation in donors and recipients who are HCV

positive [17,191]. Interferon with or without ribavirin is used for treatment of hepatitis C [192,193].

Polyomaviruses

JC virus (JVC) which belongs to polyomavirus family is known a pathogen of progressive multifocal leukoencephalopathy (PML) in patients with HIV infection. Reports of PML are quite rare in the recipients of allo-HSCT [194]. Currently, treatment and prevention of JCV in HSCT recipients remain unclear. Treatments consisting of reduction of immunosuppressants, cidofovir and serotonin-reuptake inhibitor as well as of JCV-specific CTL infusion were demonstrated to produce a favorable clinical outcome [194].

As mentioned, BKV as a member of polyomavirus family is one of the causes of HC in allo-HSCT recipients. It is reported that ciprofloxacin and other fluoroquinolones may be useful to prevent BKV reactivation [195]. Cidofovir has been used in the treatment of BKV-associated HC [196,197].

Conclusion

Viral diseases are important complications after HSCT. Development of viral diagnostics improves the early diagnosis and increases the diagnostic rate of some newly discovered or uncommon viruses in allo-HSCT recipients. Based on the pathogenesis of viral diseases, prophylaxis, especially preemptive therapy can limit reactivation of some latent viruses. Immunotherapeutic strategies to restore virus-specific immunity are attractive methods in the treatment of viral diseases.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

The manuscript is derived from literature summarizing reports prepared by RL and QFL. Both authors wrote the manuscript and have read and approved the final version.

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VACCINE INFORMATION STATEMENT

Your Baby's First Vaccines

What You Need to Know

Many Vaccine Information Statements are available in Spanish and other languages. See www.immunize.org/vis

Hojas de información sobre vacunas están disponibles en español y en muchos otros idiomas. Visite www.immunize.org/vis

Your baby will get these vaccines today:

☐ DTaP ☐ Polio

☐ Hib ☐ PCV13

☐ Hepatitis B

(Provider: Check appropriate boxes.)

1 Why get vaccinated?

These vaccines can protect your baby from 7 childhood diseases:

1. Diphtheria

Signs and symptoms include a thick coating in the back of the throat that can make it hard to breathe.

Diphtheria can lead to breathing problems, paralysis and heart failure.

- About 15,000 people died each year in the U.S. from diphtheria before there was a vaccine.

2. Tetanus (Lockjaw)

Signs and symptoms include painful tightening of the muscles, usually all over the body.

Tetanus can lead to stiffness of the jaw that can make it difficult to open the mouth or swallow.

- Tetanus kills 1 person out of every 5 who get it.

3. Pertussis (Whooping Cough)

Signs and symptoms include violent coughing spells that can make it hard for an infant to eat, drink, or breathe. These spells can last for several weeks.

Pertussis can lead to pneumonia, seizures, brain damage, or death.

4. Hib (*Haemophilus influenzae* type b)

Signs and symptoms can include fever, headache, stiff neck, cough, and shortness of breath. There might not be any signs or symptoms in mild cases.

Hib can lead to meningitis (infection of the brain and spinal cord coverings); pneumonia; infections of the blood, joints, bones, and covering of the heart; brain damage; and deafness.

- Before there was a vaccine, Hib disease was the leading cause of bacterial meningitis in children under 5 years of age in the U.S.

5. Hepatitis B

Signs and symptoms include tiredness, diarrhea and vomiting, jaundice (yellow skin or eyes), and pain in muscles, joints and stomach. But usually there are no signs or symptoms at all.

Hepatitis B can lead to liver damage, and liver cancer. Some people develop chronic (long term) hepatitis B infection. These people might not look or feel sick, but they can infect others.

- Hepatitis B can cause liver damage and cancer in 1 child out of 4 who are chronically infected.

6. Polio

Signs and symptoms can include flu-like illness, or there may be no signs or symptoms at all.

Polio can lead to permanent paralysis (can't move an arm or leg, or sometimes can't breathe) and death.

- In the 1950s, polio paralyzed more than 15,000 people every year in the U.S.

7. Pneumococcal Disease

Signs and symptoms include fever, chills, cough, and chest pain.

Pneumococcal disease can lead to meningitis (infection of the brain and spinal cord coverings), blood infections, ear infections, pneumonia, deafness, and brain damage.

These diseases are much less common than they used to be. But the germs that cause them still exist, and even a disease that has almost disappeared will come back if we stop vaccinating. This has already happened in some parts of the world. **When fewer babies get vaccinated, more babies get sick**.

Babies usually catch these diseases from other children or adults, who might not even know they are infected. A mother with **Hepatitis B** can infect her baby at birth. **Tetanus** enters the body through a cut or wound; it is not spread from person to person.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Five Childhood Vaccines can protect your baby from these seven diseases:

Vaccine	Number of doses	Recommended ages	Other information
DTaP (diphtheria, tetanus, pertussis)	5	2 months, 4 months, 6 months, 15-18 months, 4-6 years	Some children should not get pertussis vaccine. These children can get a vaccine called DT (diphtheria & tetanus).
Hepatitis B	3	Birth, 1-2 months, 6-18 months	
Polio	4	2 months, 4 months, 6-18 months, 4-6 years	An additional dose of polio vaccine may be recommended for travel to certain countries.
Hib (*Haemophilus influenzae* type b)	3 or 4	2 months, 4 months, (6 months), 12-15 months	There are several Hib vaccines. With one of them the 6-month dose is not needed.
PCV13 (pneumococcal)	4	2 months, 4 months, 6 months, 12-15 months	Older children with certain health conditions may also need this vaccine.

Your healthcare provider might offer some of these vaccines as **combination vaccines** — several vaccines given in the same shot. Combination vaccines are as safe and effective as the individual vaccines, and can mean fewer shots for your baby.

2 Some children should not get certain vaccines

Most children can safely get all of these vaccines. But there are some exceptions:

- A child who is sick on the day vaccinations are scheduled might be asked to come back for them at a later date.
- Any child who had a life-threatening allergic reaction after getting a vaccine should not get another dose of that vaccine.

  A child who has a severe (life-threatening) allergy to a substance should not get a vaccine that contains that substance. Some of these vaccines contain neomycin, streptomycin, yeast, lactose, sucrose, or latex.

  Tell your doctor if your child has any severe allergies, or has ever had a severe reaction after any vaccination.

Talk to your doctor before your child gets…

…DTaP vaccine, if your child ever had any of these reactions after a previous dose of DTaP:

- A brain or nervous system disease within 7 days,
- Non-stop crying for 3 hours or more,
- A seizure or collapse,
- A fever of over 105°F.

…Polio vaccine, if your child has a severe allergy to the antibiotics neomycin, streptomycin or polymyxin B.

…Hepatitis B vaccine, if your child has a severe allergy to yeast.

…PCV13 vaccine, if your child has a severe allergy to yeast, or ever had a severe reaction after a dose of DTaP (or other vaccine containing diphtheria toxoid), or after a dose of PCV7, an earlier pneumococcal vaccine.

3 Risks of a Vaccine Reaction

Vaccines, like medicines, can cause side effects.

Most vaccine reactions are **not serious**: tenderness, redness, or swelling where the shot was given; or a mild fever. These occur soon after the shot is given and go away within a day or two. They happen with up to about half of vaccinations, depending on the vaccine.

Polio, **Hepatitis B** and **Hib Vaccines** have been associated only with these kinds of mild reactions.

Other childhood vaccines have been associated with additional problems:

DTaP Vaccine

Mild Problems: Fussiness (up to 1 child in 3); tiredness or poor appetite (up to 1 child in 10); vomiting (up to 1 child in 50); swelling of the entire arm or leg for 1-7 days (up to 1 child in 30) — usually after the 4th or 5th dose.

Moderate Problems: Seizure (1 child in 14,000); non-stop crying for 3 hours or longer (up to 1 child in 1,000); fever over 105°F (1 child in 16,000).

Serious problems: Long term seizures, coma, lowered consciousness, and permanent brain damage have been reported following DTaP vaccination. These reports are rare.

Pneumococcal Vaccine

Mild Problems: Drowsiness or temporary loss of appetite (about 1 child in 2 or 3); fussiness (about 8 children in 10).

Moderate Problems: Fever over 102.2°F (about 1 child in 20).

Problems that could happen after any vaccine:

- Brief fainting spells can happen after any medical procedure, including a vaccination. Sitting or lying down for about 15 minutes can help prevent fainting, and injuries caused by a fall.
- Severe shoulder pain and reduced range of motion in the arm where a shot was given can happen, very rarely, after a vaccination.
- Severe allergic reactions from a vaccine are very rare, estimated at less than 1 in a million doses. If one were to occur, it would usually be within a few minutes to a few hours after the vaccination.

As with any medicine, there is a very remote chance of a vaccine causing a serious injury or death.

The safety of vaccines is always being monitored. For more information, visit: **www.cdc.gov/vaccinesafety/**

4 What if there is a serious reaction?

What should I look for?

- Look for anything that concerns you, such as signs of a severe allergic reaction, very high fever, or behavior changes.

  Signs of a severe allergic reaction can include hives, swelling of the face and throat, difficulty breathing, a fast heartbeat, dizziness, and weakness. These would usually start a few minutes to a few hours after the vaccination.

What should I do?

- If you think it is a severe allergic reaction or other emergency that can't wait, call 9-1-1 or get the person to the nearest hospital. Otherwise, call your doctor.
- Afterward, the reaction should be reported to the Vaccine Adverse Event Reporting System (VAERS). Your doctor should file this report, or you can do it yourself through the VAERS web site at **www.vaers.hhs.gov**, or by calling **1-800-822-7967**.

VAERS does not give medical advice.

5 The National Vaccine Injury Compensation Program

The National Vaccine Injury Compensation Program (VICP) is a federal program that was created to compensate people who may have been injured by certain vaccines.

Persons who believe they may have been injured by a vaccine can learn about the program and about filing a claim by calling **1-800-338-2382** or visiting the VICP website at **www.hrsa.gov/vaccinecompensation**. There is a time limit to file a claim for compensation.

6 How can I learn more?

- Ask your doctor.
- Call your local or state health department.
- Contact the Centers for Disease Control and Prevention (CDC):
  - Call **1-800-232-4636** (**1-800-CDC-INFO**)
  - Visit CDC's website at **www.cdc.gov/vaccines** or **www.cdc.gov/hepatitis**

Vaccine Safety

Vaccine Safety and Human Genetic Variations

Serious health problems following vaccination are rare, even though millions of people are vaccinated every year in the United States. Why do only a small number of people develop these health problems called vaccine-associated adverse events (VAEs)? Do they have genetically determined differences in their immune responses to vaccination, compared to those who do not experience adverse events?

Few studies have been published on the genetic risk factors for VAEs. CDC has lead responsibility for monitoring the safety of vaccines licensed for use in the U.S., and for performing research to inform safe vaccination practices. So CDC is working with partners to study the relationship between human genetics and vaccine safety.

Identifying genetic associations and risk of serious VAEs eventually may allow–

- Screening for makers of susceptibility.
- Improved guidance for vaccination.
- Development of safer vaccines.

ISO's Genomics Initiative

CDC's Immunization Safety Office (ISO) is developing a genomics initiative to–

- Develop a scientific approach to understanding the genetic basis for VAEs and their proper public applications.
- Increase cooperation between federal agencies, academia, and industry.
- Perform studies to identify genes that may be associated with an increased risk for VAEs.
- Identify strategies for integrating genomics into vaccine safety.

This initiative's long-term goal is to identify genetic features that can be determined before vaccination, so doctors can tailor vaccine schedules to the patient's personal risk.

On January 30 and 31, 2008, ISO held a conference titled "Understanding the Genomic Basis of Vaccine Safety" that brought together representatives of CDC, the Food and Drug Administration, the Department of Defense's Vaccine Healthcare Centers Network, research universities, and vaccine manufacturers. The conference discussed a systematic approach to research into the genetics of immunization safety.

Studies

There is increasing appreciation for how human genetic variation may affect the risk for medication-related and vaccine-related adverse events. While substantial research has been done on the genetic basis of medication safety, relatively little research has been done on the genetic basis of vaccine safety. ISO has sponsored five projects on this issue:

- **Evaluation of Genetic Risk Factors for Guillain-Barré Syndrome (GBS) After Vaccination.** GBS has been associated with 1976 swine influenza vaccine and the trivalent inactivated influenza vaccine in some seasons. Since GBS is rare, genetic predisposition may be an

important contributing factor. This study will identify genes that may be associated with an increased risk of GBS after vaccination.

- **A Genome-Wide Association Study to Examine Genes Associated with an Increased Risk of Febrile Seizure in Children Following Measles-Containing Vaccines.** The objective of this case-control study is to evaluate the human genome of individuals who experienced a febrile seizure 7 to 10 days after Measles-Mumps-Rubella (MMR)or Measles-Mumps-Rubella-Varicella (MMRV) vaccines in order to identify genetic risk factors associated with febrile seizures.
- **Genetic Polymorphisms and Hypersensitivity Reactions to Vaccines.** The aims of this case-control study include evaluating the role of gelatin and other components in hypersensitivity reactions to vaccines and to identify the genetic basis of hypersensitivity reactions.
- **Atopy History and the Genomics of Wheezing after Influenza Vaccination in Children 6-59 Months of Age** Miller EK, Dumitrescu L, Cupp C, Dorris S, Taylor S, Sparks R, Fawkes D, Frontiero V, Rezendes AM, Marchant C, Edwards KM, Crawford DC. *Vaccine*. 2011 Apr 18;29(18):3431-7 http://www.ncbi.nlm.nih.gov/pubmed/21396408 (http://www.ncbi.nlm.nih.gov/pubmed/21396408) (http://www.cdc.gov/Other/disclaimer.html)
- **Post-Vaccine Adverse Events: Establishment of a Centralized Repository of Biological Specimens.** CISA created a registry of clinically significant adverse events and related clinical data, and a repository of biological specimens from patients who experienced serious VAEs.

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