Respiratory virus-induced heterologous immunity

Part of the problem or part of the solution?

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Abstract

Purpose To provide current knowledge on respiratory virus-induced heterologous immunity (HI) with a focus on humoral and cellular cross-reactivity. Adaptive heterologous immune responses have broad implications on infection, autoimmunity, allergy and transplant immunology. A better understanding of the mechanisms involved might ultimately open up possibilities for disease prevention, for example by vaccination.

Methods A structured literature search was performed using Medline and PubMed to provide an overview of the current knowledge on respiratory-virus induced adaptive HI.

Results In HI the immune response towards one antigen results in an alteration of the immune response towards a second antigen. We provide an overview of respiratory virus-induced HI, including viruses such as respiratory syncytial virus (RSV), rhinovirus (RV), coronavirus (CoV) and influenza virus (IV). We discuss T cell receptor (TCR) and humoral cross-reactivity as mechanisms of HI involving those respiratory viruses. Topics covered include HI between respiratory viruses as well as between respiratory viruses and other pathogens. Newly developed vaccines which have the potential to provide protection against multiple virus strains are also discussed. Furthermore, respiratory viruses have been implicated in the development of autoimmune diseases, such as narcolepsy, Guillian–Barré syndrome, type 1 diabetes or myocarditis. Finally, we discuss the role of respiratory viruses in asthma and the hygiene hypothesis, and review our recent findings on HI between IV and allergens, which leads to protection from experimental asthma.

Conclusion Respiratory-virus induced HI may have protective but also detrimental effects on the host. Respiratory viral infections contribute to asthma or autoimmune disease development, but on the other hand, a lack of microbial encounter is associated with an increasing number of allergic as well as autoimmune diseases. Future research might help identify the elements which determine a protective or detrimental outcome in HI-based mechanisms.

Keywords Respiratory virus · Cross-reactivity · Adaptive immunity · Autoimmunity · Asthma

Abbreviations

ACTH Adrenocorticotropin
Ad Adenoviruses
ADEM Acute disseminated encephalomyelitis
APC Antigen presenting cell
BRSV Bovine RSV
CD Celiac disease
CMV Cytomegalovirus
COBRA Computationally optimized broadly reactive antigen
COPD Chronic obstructive pulmonary disease
CoV Coronavirus
CV Coxsackie virus
EAE Experimental autoimmune encephalomyelitis
EBV Epstein–Barr virus
F Anti-fusion protein
G Anti-attachment glycoprotein
GBS Guillian–Barré syndrome
GM3 Monosialodihexosylganglioside
HCV Hepatitis C virus

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HCV-SN  HCV seronegative
HDM  House dust mite
HI  Heterologous immunity
HIV  Human immunodeficiency virus
HLA  Human leukocyte antigen
HMPV  Human metapneumovirus
HPV  Human papilloma viruses
IFN  Interferon
IL  Interleukin
IM  Infectious mononucleosis
IV  Influenza virus
kDa  Kilodalton
LAIV  Live attenuated influenza vaccine
LRTI  Lower respiratory tract infections
mAb  Monoclonal antibody
MBP  Myelin basic protein
MERS  Middle East respiratory syndrome
MHC  Major histocompatibility complex
MOG  Myelin oligodendrocyte protein
MYHC  Myosin heavy chain
NKT  natural killer T
NMDAR  Anti-N-methyl-D-aspartate receptor
OVA  Ovalbumin
pMHC  peptide-MHC
rRBD  Recombinant receptor binding-domain
RSV  Respiratory syncytial virus
RTI  Respiratory tract infections
RV  Rhinovirus
S  Spike
SARS  Severe acute respiratory syndrome
SLE  Systemic lupus erythematosus
SS  Sjögren’s syndrome
T1DM  Type 1 diabetes mellitus
TCR  TCR
T_{em}  T effector memory cells
TLR2  Toll-like receptor 2
T_{m}  T memory
TRIB2  Tribbles homolog 2
T_{res}  Tissue resident memory
URTI  Upper respiratory tract infections
VP  Viral capsid proteins

**Introduction**

Respiratory viruses, such as respiratory syncytial virus (RSV), rhinovirus (RV) and influenza virus (IV) frequently cause upper (URTI) and lower respiratory tract infections (LRTI). Such infections include the common cold, pneumonia, bronchitis and bronchiolitis.

Direct and indirect costs associated with viral respiratory tract infections other than IV add up to $40 billion annually in the USA [1]. The annual burden due to IV epidemics is estimated to be around $87 billion in the USA [2]. Seasonal IV epidemics affect about 1 billion of the global population and cause up to half a million deaths every year (WHO). A viral aetiology is found in ~70% [3] of all common cold cases, while RV alone accounts for ~50% [3]. Furthermore, RV was detected in 9% of patients hospitalized for severe community-acquired pneumonia, i.e. more often than IV (6%) or *Streptococcus pneumoniae* (5%) in the same study [4].

Especially children, adults >65 years of age and the chronically ill are at high risk of developing severe disease upon LRTI. Acute LRTI are one of the major causes of childhood mortality worldwide [5]. RSV and IV are among the main pathogens causing acute LRTI in children under 5 years with at least 53 million cases of acute- and 4.4 million cases of severe acute LRTI annually [6, 7].

Viral RTI, especially RV infection, frequently cause chronic obstructive pulmonary disease (COPD) [8] and asthma [9] exacerbations. Respiratory viruses have also been implicated in the development and persistence of asthma [9, 10] as well as the initiation of autoimmune disease [11]. Despite the large impact on society, treatment of these viral infections is mostly supportive.

We discuss respiratory virus-induced adaptive heterologous immune mechanisms in infections, autoimmunity and asthma. Specifically, we describe published data in the involved virus strains, implicated T/B cell epitopes and final outcome among others. A better understanding of heterologous immunity (HI) potentially leads to new therapeutic or preventive strategies for a range of immunologically mediated disorders.

**Heterologous immunity**

HI is the altered immune response towards an antigen as a result of a preceding encounter with an unrelated antigen. Thus, immune memory is a central requirement for HI. Therefore, heterologous immune responses have exclusively been linked to the adaptive immune system. However, in recent years, innate immune memory has been described [12] and some vaccines have been associated with substantial innate heterologous effects [13]. Heterologous innate immune stimulation is a way to alter adaptive immune responses towards an antigen. This involves the induction of tolerance, Th polarization, substitution, breaking of tolerance or enhancement of adaptive immune cell responses, while maintaining antigen specificity (see Fig. 3; [14]).

Both, B and T cells have been shown to mediate heterologous effects. Antibodies have been shown to protect from heterologous virus challenge [15]. On the other hand, antibodies induced by viral infection contribute to autoimmune disease [11] and possibly play a role in alloreactivity [16]. Evidence suggests that T cell receptor (TCR) cross-reactivity is common between respiratory viruses [17–20], but it has also been shown between unrelated viruses [21–23] and even between viruses and other microbial species [23]. Cross-reactive T cells were shown to protect from heterologous virus challenge [18, 20]. Furthermore,
pathogen-derived mimics of a tumor-associated antigen are able to enhance the T cell response towards the tumor antigen [24]. Therefore, pathogen-derived epitopes might be used in a tumor vaccine. HI also has detrimental effects on the host. For example, pre-existing T memory (Tm) cells can restrict the priming of protective naive T cells to heterologous antigen [25]. Furthermore, pre-existing Tm cells can narrow the primary T cell response by shifting towards proliferation of high affinity clones only [26]. A narrowed T cell response may lead to escape variants and has been shown to be associated with severe disease progression [27, 28]. Furthermore, virus-mediated TCR cross-reactivity has also been shown to involve allo- [16] as well as autoantigens [11, 29]. Cross-reactive CD8+ T cells contributed to transplant rejection in many [16], although not all cases [30].

Unspecific activation of Tm cells has also been associated with HI in some settings. Different mechanisms have been suggested for unspecific T cell activation, e.g. IL-15 [31], IL-12 and IL-18 [32], type I interferon (IFN) [33] and type II IFN [34] signalling (Fig. 1). Bystander activated Tm cells can contribute to early pathogen control [32, 35]. Tissue resident memory (Tm) cells have an important role in pathogen clearance in the lungs. Since Tm stay at the site of infection after pathogen clearance, they provide rapid protection upon homologous virus challenge in mice [36] and humans [37]. Lung Tm were shown to protect from heterosubtypic IV challenge in mice [38, 39]. Of note, HI may alter the immunodominance, induce changes in Th polarisation or result in loss of specific Tm cells [28]. In addition, heterologous immune responses are not necessarily reciprocal [40].

**Cellular/humoral cross-reactivity**

T cells are equipped with TCRs, with whom they sense their cognate antigen. Major histocompatibility complex (MHC) molecules present peptide antigen to T cells in the form of peptide-MHC (pMHC) complexes. MHC I molecules present peptides 8- to 14-mers of length [41]. The estimated number of divergent TCRs in the human native T cell pool is <10^8 [42], whereas the number of potential foreign peptides presented by MHC molecules is suggested to be >10^15 [41]. Taken together, broad TCR cross-reactivity is inevitable for sufficient immune protection [41, 43]. This theory is further supported by the finding that one TCR is able to recognize >1 million different peptides presented by one MHC molecule [44]. Cross-reactivity is common between peptides with a high degree of sequence homology [23, 45–47], but also peptides with little homology are able to elicit cross-reactive immune responses [29, 48–51]. Moreover, TCR cross-reactivity is restricted to peptides of the same length, when presented via MHC class I [52]. Cross-recognition between seemingly non-related peptides might occur due to hotspot binding, where
the peptide–TCR interaction is focused on a hotspot, while tolerating substitutions in other positions [53].

B and plasma cells contribute to host protection by producing antibodies, which can neutralize pathogens and/or toxins. The recognition of antigen occurs at the binding cleft of the antibody, which is located in the fragment antigen binding (Fab) domain. The binding cleft contains multiple paratopes, which recognize B cell epitopes on antigens [54]. Therefore, all antibodies are potentially polyspecific [54], which might be necessary to provide sufficient immune protection against the majority of pathogens. B cell epitopes constitute of 15 amino acids on average [55] and most of them are, in contrast to T cell epitopes, conformational or discontinuous epitopes [56]. In addition, hotspot recognition is also likely in antibody–antigen interaction [56].

Heterologous immunity between respiratory viruses

Coronaviruses (CoV)

Middle East respiratory syndrome (MERS)-CoV and severe acute respiratory syndrome (SARS)-CoV caused recurrent epidemics, which were associated with a high mortality. CD4+ and CD8+ T cells as well as antibodies have all been suggested to have protective effects against SARS-CoV infection [57]. Humoral cross-reactivity between SARS- and MERS-CoV was absent in several studies [58]. But recently, Tai et al. [59] showed that immunization of mice with recombinant receptor binding-domain (rRBD) of the spike (S) protein from different MERS-CoV strains induced broadly neutralizing antibodies against up to 17 human and camel MERS-CoVs. Intranasal vaccination with a viral vaccine vector, which encodes a conserved SARS-CoV CD4+ T cell epitope protected mice from homologous and heterologous challenge with MERS-CoV. Protection was dependent on cross-reactive CD4+ T cells, producing IFNγ [60].

Influenza virus (IV)

CD4+ and CD8+ T cells generated in a preceding IV infection or vaccination are able to provide protection against heterosubtypic IV infection in humans [18, 20] or mice [17]. T cells cross-strain protection is due to recognition of conserved IV proteins. Seasonal IV vaccines generate strain-specific neutralizing antibodies against HA and NA, but fail to induce a significant cross-reactive response. Therefore, a major goal is to develop IV vaccines, which induce a cross-reactive T cell and/or antibody response.

One target might be the immunodominant HLA (human leukocyte antigen)-A2-M158 epitope, which is conserved over strains for many years, although mutations were detected [47]. Valkenburg et al. [47] showed that M158-specific CD8+ T cells also recognized three naturally occurring M158 peptide variants. In addition, M158-specific Tm cells from unexposed adults lysed IV A H1N1 2009 pandemic (A(H1N1)pdm09) infected cells ex vivo [61]. Therefore, the M158 epitope is a potential target for a broadly IV protective vaccine.

Prime-boost vaccination with the licenced live attenuated influenza vaccine (LAIV) conferred enhanced protection against heterosubtypic IV A challenge compared to FluZone or control. Protection was dependent on CD4+CD8+ T cells, which also protected against heterosubtypic challenge [62]. In addition, the 2014–2015 and 2015–2016 seasons LAIV vaccine induced lung CD4+ CD44+ CD62L+ CD69+ Tm cells in C57BL/6 mice [39]. Mice were protected against heterosubtypic challenge for up to 45 weeks [39]. LAIV vaccination was also shown to boost pre-existing cross-reactive T cells in 50% of vaccinated children [63].

Vaccination with self-amplifying mRNA (SAM®) (GlaxoSmithKline, London, UK) in lipid nanoparticles, encoding for conserved internal IV A proteins (nucleoprotein [NP] and/or matrix protein 1 [M1]), induced proliferation of NP- and M1-specific CD4+ Th1 cells as well as NP147–155-specific CD8+ T cells in mice. All vaccinated mice survived heterosubtypic IV A challenge [64]. Evidence suggests that innate immune stimulation leads to a broader adaptive immune response [64]. A Toll-like receptor 2 (TLR2) agonist together with a split IV vaccine, but not vaccine alone, protected mice against homologous and heterologous virus challenge. Heterologous effects were dependent on CD8+ T cells specific for NP147–155 [65].

The HA consists of the highly variable globular head domain, which is the main target of the antibody response, and the stalk/stem domain. The stalk domain is highly conserved among two groups in IV A [66]. Anti-stalk antibodies occur in lower titers and less frequent than anti-head antibodies and are infrequently induced by inactivated IV vaccines [66, 67]. An inactivated H5N1 vaccine showed on average a fourfold anti-stalk antibody increase in humans after the first immunization [67]. Different approaches for a stalk vaccine are under investigation and hold promise for a universal IV vaccine [68].

Computationally optimized broadly reactive antigen (COBRA) vaccines of the HA head domain have the potential to generate broadly protective antibodies. Seasonal and pandemic-derived H1N1 COBRA HAs with the broadest HA activity were inoculated into mice, using virus-like particles (VLP). Vaccination induced broadly reactive antibodies and protected mice from A(H1N1)pdm09 challenge [69].

Another approach to overcome strain-specific immunity are vaccines containing the highly conserved extracellular domain of the IV matrix protein 2 (M2e). Many different VLPs are used to enhance the otherwise low immunogenicity of M2e [70]. Different M2e-based vaccines induced anti-M2e antibodies [38, 70],
but also CD4+ or CD8+ T cells [71, 72], which were protective against heterologous virus challenges in mice. Furthermore, M2e-VLP induced lung CD8+ Tm cells, which mediated long-lived (>4 months) heterologous protection in mice [38]. Different M2e vaccines [70] and an anti-M2e monoclonal antibody (mAb) [73] were safe in human trials, but immunity can still be improved.

Respiratory syncytial virus (RSV)

In response to RSV infection, the anti-fusion (F) protein and anti-attachment glycoprotein (G) are the main antibodies produced [74, 75]. CD8+ T cells contribute to RSV clearance in murine models [74] and lung CD8+ Tm cells have protective effects in human RSV challenge [37]. No vaccine is currently available against RSV, although many approaches for a broadly protective vaccine have been discussed [74]. Vaccination of mice with a recombinant fusion protein, containing a conserved region of the G protein (131-230) of RSV-A and RSV-B strains, resulted in IgA and IgG antibodies specific for both RSV-A and RSV-B G proteins. This vaccination protected mice from challenge with RSV-A or RSV-B [76]. The calf animal model is closer to RSV infection in humans. Taylor et al. [77] vaccinated calves with viral vectors expressing sequences of the F, N and M2-1 proteins of human RSV (HRSV). The vaccination induced neutralizing antibodies as well as CD4+ IFNγ+ T cells. Calves were protected from heterologous bovine RSV (BRV) challenge, possibly because of cross-reactivity, since HRSV and BRV have a high degree of sequence homology. Cross-reactivity of human antibodies has also been detected between two epitopes of the G-protein of RSV-A and RSV-B. Such human IgG antibodies showed neutralizing effects against both viruses in HEP-2 cell culture [75]. Furthermore, human mAbs, cross-neutralizing RSV and human metapneumovirus (HMPV), have been identified [15, 78]. One of these mAbs also reacted to two other paramyxoviruses [15], while protective effects upon infection with the aforementioned viruses in murine models have been described [15, 78].

Rhinovirus (RV)

Infection with RV generates serotype-specific antibodies, which can prevent infection with the same serotype. Since there are over 160 distinct RV strains characterized to date [9], reinfection with other strains is common. Viral capsid proteins (VP) of RV contain sequences [79] and T cell epitopes [80], which are conserved across strains. Therefore, humoral or cellular cross-reactivity might provide cross-strain protection against heterologous RV infection.

Immunization with RV-A16-derived VP0 and a Th1 promoting adjuvant protected mice from heterologous RV-A1B challenge [9, 79]. CD4+ Th1 cells were preferentially expanded. Lung T cells from immunized and RV-A1B-infected mice showed increased IFNγ production compared to control, upon stimulation with RV-A16 VP0 and heterologous RV14 and RV-A1B-VP0 peptides. Immunization also enhanced neutralizing antibodies in heterologous RV challenge. Cross-reactive IgG1 VP1-specific antibodies, especially between RV-A and -C, have been detected in humans [81]. Limitations might arise from the fact that some antibodies bind nonprotective epitopes, which might lead to immune escape of RV [82]. Seronegative, healthy humans have CD4+ and CD8+ T cells against RV-A39 epitopes [19]. Co-culture of DCs, RV-A39 and T cells resulted in proliferation of CD4+ and CD8+ T cells and enhanced IFNγ production. Muehling et al. [80] showed that pre-existing CD4+ Tm cells, specific to conserved epitopes of the VP region, proliferate upon RV-A16 challenge in seronegative donors. CD4+ Tm cells mainly showed a Th1 or T follicular helper phenotype. Furthermore, RV-A16 VP2162–181-specific T cells, also recognized the VP2169–188 epitope of RV-A39. The results suggest that Tm cells specific for conserved RV regions may mediate heterologous protection. Conserved sequences might be used in a peptide vaccine, which could be especially useful in asthmatics or COPD patients.

Heterologous immunity between respiratory and other viruses

Epstein–Barr virus (EBV)

EBV is the causative pathogen of infectious mononucleosis (IM), the disease severity of which varies substantially. Children usually show mild to no symptoms, whereas adolescents and adults often present with more severe symptoms. Reactivation of IV-M158-specific CD8+ T cells, which are cross-reactive to the EBV BamHI M fragment leftward open reading frame 1280–288 (BMLF1280) epitope were shown to contribute to lymphoproliferation in IM ([48]; Table 1). In addition, frequency of IV-M158 and M158-EBV BMLF1280 tetramer+ CD8+ T cells correlated with IM disease severity [83]. This was associated with different TCR repertoire usage and enhanced IFNγ production. Others found bystander activation, but no expansion of IV-specific CD8+ T cells in IM [84]. BMLF1280-specific CD8+ T cells of human donors were shown to recognize up to two IV-derived and two EBV-derived epitopes [49]. Private TCR repertoire usage might explain differences in the number of peptides recognized by BMLF1280-specific CD8+ T cells between donors [49]. Recent data suggest that T cell cross-reactivity between IV-M158, and BMLF1280 and BamH1 R fragment leftward open reading frame 1109–117 protects some adults from primary EBV infection [85]. Seronegative status was associated with usage of a private oligoclonal TCR repertoire and higher frequency of CD103+ IV-M1-specific T cells. The authors spec-
ulate that cross-reactive T\textsubscript{rm} might prevent primary EBV infection of B cells in the tonsils.

**Hepatitis C virus (HCV)**

Acute HCV infection is variable in its symptoms, ranging from asymptomatic to severe disease. The HLA-A2 restricted nonstructural protein 3\textsubscript{1073–1081} (NS3\textsubscript{1073}) epitope of HCV is a target for CD8\textsuperscript{+} T cells in HCV infection. NS3\textsubscript{1073}-specific T cells were detected in the blood of HCV positive donors, but also in HCV seronegative (HCV-SN) donors [22, 86]. Further analysis showed first that NS3\textsubscript{1073}-specific T cells are cross-reactive to NA\textsubscript{231–239} epitope and second that IV infection induced HCV specific T cells [22]. Another study found the cross-reactivity between those epitopes to be weak and recognition of the NA\textsubscript{231–239} epitope was dependent on preceding HCV infection [87]. NS3\textsubscript{1073}-reactive T cells were shown to be cross-reactive to cytomegalovirus-(CMV), Epstein–Barr virus-(EBV)-derived and the IV M\textsubscript{158} epitopes in vitro [86]. Therefore, NS3\textsubscript{1073}-reactive T cells might originate from infection with one of these viruses. Pre-existing cellular immunity towards the NS3\textsubscript{1073} epitope can either result in an enhanced immunity, as shown in evaluation of a HCV peptide vaccine trial [86], or have detrimental effects, as shown by Urbani et al. [27]; Table 1]. The latter found that patients with severe HCV liver disease used a private TCR repertoire, with T cells cross-reactive to NA\textsubscript{231–239} and NS3\textsubscript{1073} epitopes. In those patients the CD8\textsuperscript{+} T cell response was narrowly focused on the NS3\textsubscript{1073} epitope [27].

Adenoviruses (Ad) are known for their potential as viral vectors in vaccination against infection [88] and have also been utilized for gene therapy [89]. Inoculation of Ad serotype 5 (Ad5) into mice induced robust humoral and cellular immunity against multiple HCV peptides in vitro and resulted in enhanced virus clearance [90]. Moreover, HCV-SN donors with pre-existing Ad immunity showed cross-reactive humoral and cellular immunity towards HCV peptides [90]. Further studies are needed to determine the possible use of Ad in the development of a vaccine for HCV. Limitations may arise from pre-existing Ad immunity, which possibly leads to lack of response to vaccination.

**Human immunodeficiency virus (HIV)**

T cell cross-reactivity was detected for the HLA-A2 restricted IV-M\textsubscript{158} and the HIV-1 p17 GAG\textsubscript{77–85} epitopes in vitro, among both HIV seropositive and seronegative donors ([21]; Table 1]. Cross-reactivity was weak in some seronegative donors, which suggests that a strong T cell response to the IV-M\textsubscript{158} is necessary to induce HIV-1 reactive T cells. A larger cohort study with 175 HIV seropositive HLA-A2\textsuperscript{+} subjects confirmed HIV-1 and IV cross-reactivity. T cells of HIV\textsuperscript{+} individuals frequently targeted the p17 GAG\textsubscript{77–85} and the IV-M\textsubscript{158} epitopes in vitro [51]. About 40% showed T cells specific for both epitopes in vitro [51]. No effect of IV and HIV cross-reactive T cells on the course of HIV infection could be detected. Adenoviral vectors are used to form an HIV vaccine. To avoid formation of strain specific antibodies, rare adenovirus strains are utilized. Unfortunately, also pre-existing cellular immunity against adenovi-

### Table 1. Heterologous immunity between respiratory and nonrespiratory viruses. Involved proteins and epitopes are listed in connection to a given MHC background

| Allele   | Respiratory virus | Respiratory virus epitope | Sequence               | Other pathogen | Other epitope | Sequence              | Outcome   | Ref |
|----------|------------------|--------------------------|-----------------------|----------------|---------------|-----------------------|-----------|----|
| HLA-A2   | CoV              | NS252–60                 | TMLDQPE\textsubscript{5} | HPV 16         | E7,11–19\textsubscript{20} | YMLDQPE\textsubscript{T} | Various   | [46] |
|          | Ad5              | –                        | –                     | HCV            | –             | –                     | Beneficial| [90] |
| C57Bl/6  |                  |                          |                       |                |               |                       |           |     |

Ad 5 Adenovirus serotype 5, BMLF1 BamHI M fragment leftward open reading frame 1, BRLF1 BamHI R fragment leftward open reading frame 1 (both from EBV-derived immediate-lytic protein), CoV Coronavirus, E7 Transforming protein E7, F. magna Finegoldia magna, EBV Epstein–Barr Virus, HAV Hemagglutinin, HCV Hepatitis C Virus, HIV Human Immunodeficiency Virus, HLA human leukocyte antigen, HPV 16 Human Papillomavirus type 16, IV Influenza Virus, M1 Matrix protein 1, NA Neuraminidase, NP Nucleoprotein, NS2 Nonstructural protein 2, NS3 Nonstructural protein 3, p17 GAG group-specific antigen/gag-derived Matrix Protein (p17), T. vaginalis Trichomonas vaginalis

bald Amino acids in common between two epitopes
Table 2  Heterologous immunity between respiratory viruses and autoantigens. Host- and virus-derived proteins as well as epitopes are listed

| Disorder   | Respiratory viruses (association) | Immune cells involved | Pathogen-derived protein | Pathogen-derived epitope sequence | Host-derived epitope | Host-derived epitope sequence | Comment | Ref |
|------------|----------------------------------|-----------------------|--------------------------|-----------------------------------|----------------------|-------------------------------|---------|-----|
| ADEM       | Ad, HMPV, HPIV, IV infection/vaccination | T cells              | IV HA                    | YRNLVWFRKKNTRYP                 | MBP85–99             | ENPVVHFFKNIVTRP               | --      | [29]|
|            |                                   |                      | Ad 12 ORF                | DFEVFILKDVLPE                    |                      | ENPVVHFFKNIVTRP               | --      |     |
|            |                                   |                      | IV HA(30–318)            | YKQONTLKLAA                     |                      |                               |         |     |
|            |                                   |                      |                          | YKQONTLKLAA                     |                      |                               |         |     |
| CD         | Ad                                | T/B cells            | Ad 54kDa E1b 384–395    | LRGMVFRPSQGQN                   |                      |                               |         |     |
| GBS        | IV infection/vaccination          | B cells              | IV HA                    | --                               | GM1                  | --                            | --      | [108]|
| Myocarditis | Ad, IV, RSV, CV                    | T cells              | CV                       | --                               | --                   | DSADFWSLFAEKAGVKY              | --      | [129]|
|            |                                   |                      |                          |                                   |                      |                               |         |     |
| Narcolepsy | IV infection/vaccination          | B cells              | IV A NP11–121 [GM3; TRIB2] | YDKEERWR                      |                      | YDDEEELRVRWR                  | --      | [111]|
| IV         |                                   | B cells              | IV HA                    | Various                           |                      |                              |         |     |
| SARS-CoV, IV |                                |                      | IV                        | --                               |                      |                              |         |     |
|            |                                   |                      | IV                        | --                               |                      |                              |         |     |
| SS         | CV                                | B cells              | Various                  | ACTH                              | ACTH                 | --                            |         |     |
| T1DM       | CV                                | B cells              | IV HA (mAbs)             | --                               |                      | Tissue staining with mAbs     |         |     |

ACTH adrenocorticotropic hormone, ADEM Acute Disseminated Encephalomyelitis, Ad Adenovirus, AGP Axon guidance proteins, CD Celiac disease, Col IV Collagen IV, CoV Coronavirus, CV Coxsackie virus, GBS Guillain–Barré Syndrome, GM1 Monosialoganglioside, GM3 Monosialodihexosylganglioside, HA Hemagglutinin, HCRTr2 Hypocretin Receptor 2, IV influenza virus, HPV Parainfluenza virus, mAbs monoclonal antibodies, MBP Myelin Basic Protein, MOG Myelin Oligodendrocyte Glycoprotein, MHC-α cardiac myosin heavy chain-α, NA Neuraminidase, NMDA A2 N-methyl-D-aspartate receptor A2 subunit, ORF Open Reading Frame, ASV Respiratory syncytial virus, SS Sjögren Syndrome, TRIB2 Tribbles homolog 2, T1DM Type 1 diabetes mellitus.

**bold** Amino acids in common between two epitopes.
ral vectors can impede successful vaccination. Frahm et al. [91] showed that pre-existing Ad5-specific CD4+ T cells led to decreased numbers of CD4+ HIV-specific T cells and to a narrowed CD8+ T cell response upon Ad5-based HIV vaccination in humans. In addition, extensive T cell cross-reactivity between adenovirus strains was shown. Furthermore, CD4+ HIV-cross-reactive Tm cells have been detected in unexposed adults [23], which further complicates prediction of anti-HIV immunity.

Human papilloma viruses (HPV)

High risk HPVs, such as type 16, 18 and others are the main risk factor for multiple genital cancers. Nilges et al. [46] described cross-reactivity between HLA-A2-binding epitopes E711-19/20 of HPV type 16 and the NS252–60-derived epitope of human CoV OC43 (Table 1). HPV E7-reactive CD8+ T cells were found in patients with cervical cancer and even more often in healthy blood donors. E711-19/20-reactive T cells in healthy donors were possibly formed in CoV infection. Whether T cell cross-reactivity here has negative effects on antitumor immunity or might support tumor clearance remains to be determined.

Heterologous immunity between respiratory viruses and pathogens other than viruses

Pre-existing HA391–410-specific CD4+ Tm cells showed expansion after seasonal IV vaccination. These Tm cells expanded after stimulation with the *Trichomonas vaginalis* (*T.vaginalis*)-derived hypothetical protein118–130 and the *Finegoldia magna* (*F. magna*)-derived hypothetical protein131–143 peptide *in vitro* (Table 1). HA391–410-specific CD4+ T cells from one donor recognized both peptides, whereas in the other donor the T cells only recognized the *F. magna* peptide. Furthermore, the two peptides stimulated different IV-reactive T cell clones with distinct affinity [23]. These results might be a result of first, differential shaping HI based on encounter with diverse pathogens and second the fact that HI is not necessarily reciprocal.

The oral live-attenuated salmonella typhi Ty21a strain vaccine induced both an increase of Ty21a-reactive and influenza-reactive T cells in the duodenal mucosa of healthy adults [92]. Homing markers were upregulated in Ty21a-reactive and influenza-reactive T cells. More studies are needed to better determine the mechanism behind the increase of influenza-specific T cells in the duodenal mucosa.

Autoimmunity

Acute disseminated encephalomyelitis (ADEM)

ADEM is preceded by either infection in up to 77% of cases [93] or vaccination in 5–10% of cases [94]. Episodes of infection or vaccine related ADEM may also occur in the same patient [95]. HMPV [96], parainfluenza [97] and IV infection [98] or IV vaccination [94] preceding ADEM, have all been reported. Influenza infection has been shown to trigger [99] or exacerbate [100] disease in experimental autoimmune encephalomyelitis (EAE) models, which might be a useful to study ADEM [101].

In patients affected by ADEM, myelin basic protein (MBP)-reactive T cells [102] as well as different neuronal antibodies, including anti-myelin oligodendrocyte protein (MOG) have been detected [103]. Generation of these autoreactive T cells and antibodies is probably due to molecular mimicry. TCR cross-reactivity between MBP/MOG-derived and respiratory virus-derived epitopes has been shown for coronavirus [104], adenovirus [29] and influenza A virus HA epitopes ([29, 50]; Table 2). Anti-MOG antibodies, which are frequently found in ADEM [103], might have a pathogenic role, since they induce demyelinating disease in EAE animal models [105].

Guillain–Barré syndrome (GBS)

About 60% of all GBS cases are thought to be infection-related [106], most frequently gastrointestinal or respiratory tract infections including influenza [98]. Molecular mimicry of antibodies against pathogen-derived and self-antigens seem to play a major role in the initiation of GBS [106] and this is best described for *Campylobacter jejuni*.

A recent meta-analysis found a slight, but significant increase in the relative risk of influenza vaccine-associated GBS among 39 studies published between 1981 and 2014 [107]. Others found no such increase in disease risk [106]. The link between influenza infection and subsequent development of GBS is better established [106].

The mechanisms of influenza- and influenza-vaccine-induced GBS largely remain unknown. A first clue might be the findings of Nachamkin et al. [108], who showed that the A/NJ/1976 (H1N1) vaccine as well as trivalent vaccines from 1992–1993 and 2004–2005 seasons induced anti-HA and also anti-GM1 antibodies in mice after immunization. In addition, the 2004–2005 vaccine contains glycolipid-like structures, as shown by positive anti-GM1 immunostaining [108]. Anti-GM1 antibodies showed a low, but detectable hemagglutination inhibition activity.

Narcolepsy

Narcolepsy was associated with the IV A(H1N1)pdm09 vaccine Pandemrix® (GlaxoSmithKline, London, UK) [109] and also with A(H1N1)pdm09 infection [110]. Recently, Ahmed et al. [111], showed that the Pandemrix® vaccine, in some HLA-DQB1*06:02-positive individuals, induced IV A NP111-121 antibodies, which were cross-reactive to the hypocretin receptor 234-45 (Table 2). Although hypocretin receptor 2 autoantibodies
were detected in 85% of patients with Pandemrix®-associated narcolepsy [111], the exact mechanism of the antibody-induced narcolepsy remains to be determined.

Other autoantibodies with a potential link to narcolepsy are anti-monosialodihexosylganglioside (GM3) [112]—and anti-Tribbles homolog 2 (TRIB2) [113] antibodies. Anti-GM3 antibodies were detected more frequently in patients with Pandemrix®-associated narcolepsy than in vaccinated healthy controls [112], whereas no such correlation was evident for anti-TRIB2 antibodies after Pandemrix® vaccination [114]. Nonetheless, anti-TRIB2 antibody titers were found to be increased in narcolepsy patients, compared to controls [113]. Furthermore, transfer of pooled anti-TRIB2 positive IgG samples from the blood of narcolepsy patients into mice resulted in narcolepsy-like symptoms and orexin-neuron loss [115].

Other neurologic/neuropsychiatric disorders

Anti-N-methyl-D-aspartate receptor (NMDAR) antibodies were detected in patients with herpes simplex encephalitis [116], although results are inconsistent [117]. These findings suggest that infections are a possible trigger for psychiatric diseases.

Maternal infection, including influenza, has been suggested to play a role in development of psychiatric disorders in the child [118]. Lucchese et al. identified influenza epitope mimics in multiple neuronal proteins ([119, 120]; Table 2). Cross-reactivity might lead to neuropsychiatric disorders, although experimental verification is needed.

Other autoantibodies, which may play a role in neuropsychiatric disorders, such as anorexia nervosa, chronic fatigue syndrome or major depression, are anti-adrenocorticotropin (ACTH) antibodies [121], which may cause ACTH deficiency. Wheatland proposed that SARS-CoV infection can induce pathogen-specific antibodies, which are cross-reactive to ACTH ([122]; Table 2).

Celiac disease (CD)

Gastrointestinal infections and to a lesser extent also respiratory infections in early life increased risk of developing CD [123]. Ad may contribute to CD development. A sequence mimic of the A-gliadin proteinH2b6–217 has been identified in the 54 kilodalton (kDa) E1b protein of Ad 12384–395 [45]. Rat antiserum generated against the E1b384–395 epitope cross-reacted with A-gliadin as well as a synthetic A-gliadin311–317 peptide ([45]; Table 2). CD patient serum antibodies were also shown to react to a synthetic A-gliadin312–317 peptide [124]. Furthermore, T cell cross-reactivity to a synthetic peptide resembling the A-gliadin/E1b sequence have been detected in CD patients [125]. These results were inconsistent in follow-up studies [126].

Myocarditis

Infectious myocarditis is caused by different pathogens, including respiratory viruses such as Ad, IV, RSV and CV [98, 127]. Viral and immune mechanisms contribute to disease onset and persistence in myocarditis [127]. Massilamany et al. [128] showed that immunization of A/J mice with peptide mimics of cardiac myosin heavy chain (MYHC)-α334–352 induced cross-reactive T cells and led to the development of myocarditis. Additionally, CV B3 infection

![Fig. 2](image-url)  
**Fig. 2**  
Influenza-mediated prevention of allergic airway inflammation was identified in two murine models of OVA- and house dust mite-induced experimental asthma. Transfer experiments revealed that protection was dependent CD4+ and CD8+ Tεm cells. Ex vivo stimulation of lung Tεm cells from H1N1-infected animals resulted in enhanced IFNγ and IL-10 release. An in silico analysis identified four influenza- and three OVA-derived potentially cross-reactive candidate T-cell epitopes. Immunization with a mixture of these identified influenza peptides conferred asthma protection. These results illustrate heterologous immunity of virus-infected subjects towards allergens, and extend the hygiene hypothesis. H1N1 influenza H1N1 virus strain, IL Interleukin, IFN Interferon, NP Nucleoprotein, OVA Ovalbumin, PA Polymerase acidic protein, PB2 Polymerase basic protein 2, Tεm T effector memory cells
Autologous innate immune stimulation

- Contact allergen
  - DAMPs, ROS, ATP, HA, others

Heterologous innate immune stimulation

- Infection
  - Other contact allergens
  - Irritants etc.
  - DAMPs, PAMPs, ROS, ATP, HA, others

Resting DC

Activated DC

T cell activation

Fig. 3  Example of heterologous innate immune stimulation in ACD. Contact allergens are able to trigger PRRs directly or indirectly by the release of mediators. Heterologous innate immune stimuli, such as infections or irritants can enhance innate immune activation and therefore promote the development of a contact allergen-specific T cell response and ACD. Allergen-specific T cells are usually raised against the autologous innate immune stimulus (contact allergen), while heterologous innate immune stimuli in most cases do not trigger a T cell response. ACD Allergic contact dermatitis ATP Adenosine triphosphate, DAMP Damage-associated molecular patterns, DC Dendritic cell, HA Hyaluronic acid, PAMP Pathogen-associated molecular patterns, ROS Reactive oxygen species, PRR Pattern recognition receptors. (Adapted from Martin SF [14])

led to the generation of such MYHC-α334–352-reactive CD4+ T cells and associated myocarditis in A/J mice ([129]; Table 2). Different antibodies, including those against cardiac myosin and actin, are associated with myocarditis [127]. CV mimics sequences of actin, myosin, collagen and laminin [130]. Moreover, anti-CV antibodies were shown to bind to actin, collagen IV and fibronectin [130].

Sjögren’s syndrome (SS)

Viral infections, including CV have been suggested to play a role in the development of SS [131]. In SS, antibodies and/or T cells to different autoantigens, frequently Ro (SSA) and La (SSB) are present [132, 133]. Sequence homologies between the 2B protein of CV A21/A13 and the Ro60 kDa antigen may induce cross-reactive autoantibodies. Statthopoulou et al. [134] showed that serum of SS patients recognized synthetic peptides from the homologous regions of both proteins more frequently than serum of systemic lupus erythematosus (SLE) patients or controls. Cross-reactivity was confirmed in inhibition assays, using both synthetic peptides ([134]; Table 2). Mimics of Ro60 kDa T cell epitopes have been identified in various bacteria from the human skin, oral cavity, intestine and vaginal flora [135]. Peptide mimics were able to stimulate Ro60 kDa-reactive T cells [135].

Type 1 diabetes mellitus (T1DM)

Development of T1DM has been linked to different viral infections, especially enterovirus infection. Also respiratory viral infections, including IV may be associated to T1DM [136]. One possible mechanism, contributing to autoimmunity in T1DM is molecular mimicry [44, 137]. CMV or rotavirus infection may induce cross-reactive T cells to pancreatic autoantigens [138, 139], whereas for coxsackie virus (CV) such findings are inconsistent [137].
Recently, Qi et al. [140] stained pancreatic tissue with monoclonal antibodies specific for different influenza HA epitopes. Two distinct antibodies were cross-reactive to human pancreatic α-cells, but not β-cells (Table 2). As shown before in mice, after almost complete diphtheria toxin-induced β-cell loss, pancreatic α-cells are able to differentiate into insulin producing cells [141]. If pancreatic α-cells are the progenitors to β-cells, influenza-induced antibodies against α-cell antigens eventually result in the onset of diabetes.

### Asthma/allergy

About 300 million people are currently affected by asthma worldwide [142], while the prevalence might rise to 1 billion in 2050 [143]. Characteristics of asthma are chronic airway inflammation, airway hyperreactivity, over production of mucus and remodelling of airways, which becomes relevant particularly in chronic disease.

One major risk factor for the development of asthma are recurrent wheezing episodes early in life, which are caused by viruses in 62–98% [144, 145] of cases. RSV or RV-induced wheezing in children <3 years, with at least one asthmatic parent, was associated with an increased risk for asthma at 6 years of age [146]. Recently, Lukkarinen et al. [145] followed up children with a severe wheezing episode for 7 years. They identified RV-induced wheezing, sensitization and eczema as risk factors for the development of atopic asthma, whereas non-atopic asthma risk factors included first wheezing at <12 months of age caused by viruses other than RV/RSV and parental smoking. Early onset asthma can resolve spontaneously, but recurrent infections with respiratory viruses over time makes spontaneous resolution less likely [10]. Therefore, viral respiratory tract infections also contribute to the persistence of asthma.

Most asthma exacerbations are also caused by respiratory viral infection, such as RV, RSV, IV, CoV, HMPV, parainfluenza virus and adenovirus [144]. RV is the pathogen detected most frequently in all age groups, whereas RSV affects mostly preschool children and IV is most prevalent in adults [144].

On the other hand, the prevailing concept to explain the rising prevalence of allergic and autoimmune diseases in industrialized countries is the hygiene hypothesis [147]. According to the latter, less frequent exposure to pathogens in early life is associated with the development of allergies [148]. Protective effects of bacteria or bacterial products on asthma development have been well characterized [148], but also viruses [149] as well as respiratory viruses, including IV [150], were shown to protect mice from asthma. Correlates of protection are induction of Th1 immune responses, e.g. by stimulation of innate immune receptors, such as Toll-like receptors [148, 151]. Viral infections were shown to protect from asthma by induction of an natural killer T (NKT) cell subset [150] or monocytes with a regulatory phenotype [149].

Our group further examined the role of respiratory viral infection on asthma protection in a murine model. In agreement to earlier reports [150, 152], we found that IV A infection of Balb/c mice confers protection against ovalbumin (OVA)-induced, but also house dust mite (HDM)-induced asthma. Protection was dependent on CD4+ and CD8+ Tem cells, which were cross-reactive to IV A- and OVA-derived peptides, as predicted by bioinformatics analysis. Upon ex vivo restimulation with the predicted influenza A- or OVA-derived peptides, lung T cells showed increased production of IL-2 and IFNγ. Furthermore, peptide immunization with the predicted virus-derived peptides also provided asthma protection through Tem cells. This is possibly due to the production of IFNγ by virus-specific T cells upon allergen challenge, as an augmented IFNγ response can protect from experimental asthma [152]. Thus, we provide evidence for Tem-mediated HI between viruses and allergens as a protective mechanism against allergic asthma ([153]; Fig. 2).

### Conclusions and outlook

HI involving respiratory viruses may have various protective, but also detrimental effects on the host. Because of differences in the private TCR repertoire, the clinical outcome of cross-reactivity between the same epitopes may be detrimental in one and beneficial in another person, as seen for example between IV and EBV [48, 85]. IV vaccination has been associated with autoimmune diseases in a few cases [94, 107, 109]. Nevertheless, an association between autoimmune disease and respiratory viral infection has been more extensively discussed. Different approaches for broadly protective vaccines are currently under investigation. Some vaccines were shown to induce lung Tem cells, the role of which in heterologous protection from respiratory tract infections is yet to be determined in humans.

Our group showed that HI between respiratory viruses and allergens protects from experimental asthma [153], thus expanding the hygiene hypothesis. Further studies are needed to determine whether HI is a broadly applicable concept between other respiratory viruses and environmental allergens. Moreover, it will be interesting to see whether any of the currently licenced or future vaccines has the potential to induce heterologous protection from viral infection as well as asthma. Recently, gammaherpesvirus infection was shown to induce regulatory monocytes, which prevented experimental asthma in mice [149]. Therefore, heterologous innate immune stimulation with tolerogenic or T1 promoting adjuvants [14] might be utilised to induce allergen tolerance (Fig. 3).
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**Appendix**

**Glossary**

**Acute disseminated encephalomyelitis (ADEM)** ADEM is a rare autoimmune disease affecting the central nervous system (CNS), with an incidence of 0.6–0.8/100,000 people/year [94]. Especially young children suffer from ADEM, but adults may also be affected. ADEM is an autoimmune mediated, demyelinating disease of the central nervous system (CNS) with a usually monophasic course. Clinically, a vast array of neurological symptoms is possible, from varying focal deficits to encephalopathy (confusion, reduced consciousness, irritability).

**Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis** Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis belongs to the heterogeneous group of autoimmune epilepsies, which mainly occur as paraneoplastic syndromes [154]. Antibodies directed against cancer antigens are thought to cross-react with neuronal antigens.

**Celiac disease (CD)** Prevalence of CD in the European population is approximately 1% [155]. Genetically susceptible individuals with a genetic background of HLA-DQ2 and/or HLA-DQ8, usually develop symptoms at childhood, although disease onset may occur later in life. Different infections are thought to promote or prevent CD development [156].

**Computationally optimized broadly reactive antigen (COBRA) HA** The HA amino acid compositions from many isolated IV A strains is analysed. The aim is to define a consensus sequence for every amino acid in the HA protein.

**Guillain–Barré syndrome (GBS)** GBS is a rare neurological disease with an incidence of 0.4–4/100,000 people per year [106]. Classical GBS, also called acute inflammatory demyelinating polyneuropathy (AIDP), is caused by an autoimmune demyelination of peripheral nerves, which leads to subacute ascending paralysis with muscle weakness and sensory deficits in the limbs. Severe cases can present with respiratory failure or autonomic instability. Axonal forms of GBS, namely AMAN and AMSAN are associated with anti-GM1 and/or anti GD1a antibodies, while in Miller Fisher syndrome and to a lesser extent also in Bickerstaff brainstem encephalitis, anti-GQ1b antibodies are found. No antibody specific for AIDP has been detected yet.

**Heterologous innate immune stimulation** The "original" or homologous pathogen/antigen often induces an adaptive immune response. Heterologous pattern recognition receptor (PRR) ligands stem from other sources than the original antigen and mostly do not induce adaptive immune responses. Heterologous PRR stimulation alters the immune response towards the homologous antigen. PRR ligands include various substances, such as vaccine adjuvants, other pathogens or commensal bacteria and endogenous ligands (e.g. hyaluronic acid) [14].

**Heterosubtypic immunity** Immunity towards one virus also provides heterologous immunity against a strain of the first virus. The term heterosubtypic immunity is mostly used when referred to IV A infection.

**Heterologous immunity (HI)** The immune response towards one antigen alters the immune response towards a subsequent encounter with an unrelated antigen. This involves allo-, auto- or allergen-derived antigens as well as pathogen-derived antigens. Heterologous antigen encounter may have protective or detrimental effects on the host.

**Myocarditis** The initial phase of the disease is thought to be mediated by direct myocardial damage through distinct agents (e.g. infection, toxins, drugs), which is followed by an immune mediated phase. Ongoing infection and/or autoimmune disease leads to chronic myocarditis [127]. Myocarditis can result in dilated cardiomyopathy or sudden cardiac death [127].

**Narcolepsy** Narcolepsy is characterized by daytime sleepiness, cataplexy and sleep attacks and affects about 30 per 100,000 people [109]. Loss of hypocretin (orexin)-producing neurons in the hypothalamus is characteristic for type 1 narcolepsy, but not for type 2 narcolepsy. Disease onset is typically between 10 and 30 years of age [109]. About 98% of patients with narcolepsy and cataplexy are HLA-DQB1*06:02 positive, which suggests a role for T cells in disease pathogenesis [109].

**Pandemrix®** Pandemrix® is a monovalent A(H1N1) pdm09 vaccine. It was broadly used in Europe during the 2009 swine flu pandemic. Pandemrix contained
much higher doses of NP than other A(H1N1)pdm09 vaccines [111].

Paratope The antigen binding region of an antibody contains multiple paratopes, which recognize their epitope on a given antigen. 

Private TCR repertoire The public TCR repertoire consists of T cell clones, which are identical for all individuals, whereas T cell clones, which are unique for an individual form the private TCR repertoire. The private TCR repertoire leads to variability in immune recognition and cross-reactivity phenomena. For example, the recognition of the same epitopes by different T cells may result in detrimental or beneficial disease outcomes in the respective hosts. 

Sjögren’s syndrome (SS) SS is characterized by lymphocyte infiltration of salivary glands (SGL). Decreased SGL function causes xerostomia and xerophthalmia. 

T cell receptor (TCR) cross-reactivity The ability of the TCR to recognize more than one antigen is referred to as TCR cross-reactivity.

Type 1 diabetes mellitus (T1DM) T1DM is characterized by autoimmune mediated loss of insulin-producing β-cells in the pancreas, while glucagon-producing α-cells and somatostatin-producing δ-cells are spared. Disease is thought to be T cell mediated, which means that autoreactive T cells attack pancreatic β-cells.

References

1. Fendrick AM, Monto AS, Nightengale B, Sarnes M. The economic burden of non-influenza-related viral respiratory tract infection in the United States. Arch Intern Med. 2003;163:487. https://doi.org/10.1001/archinte.163.4.487.
2. Molinari N-AM, Ortega-Sanchez IR, Messonnier ML, Thompson WW, Wortley PM, Weintraub E, et al. The annual impact of seasonal influenza in the US: measuring disease burden and costs. Vaccine. 2007;25:5086–96. https://doi.org/10.1016/j.vaccine.2007.03.046.
3. Mäkelä MJ, Puhakka T, Ruuskanen O, Leinonen M, Saikku P, Kimppimäki M, et al. Viruses and bacteria in the etiology of the common cold. J Clin Microbiol. 1998;36:539–42.
4. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Liebner JC, et al. Preexisting influenza-specific CD4+ T cell correlates with disease protection against influenza challenge in humans. Nat Med. 2013;19:1305–12. https://doi.org/10.1038/nm.3350.
5. Liu L, Ozal D, Perin J, Rudan L, Lawn JE, et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet. 2015;385:430–40. https://doi.org/10.1016/S0140-6736(14)61698-6.
6. Nair H, Brooks WA, Katz M, Roca A, Berkley JA, Madhi SA, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. Lancet. 2011;378:1917–30. https://doi.org/10.1016/S0140-6736(11)61051-9.
7. Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet. 2010;375:1545–55. https://doi.org/10.1016/S0140-6736(10)60206-1.
8. Wedzicha JA, Seemungal TAR. COPD exacerbations: defining their cause and prevention. Lancet. 2007;370:786–96. https://doi.org/10.1016/S0140-6736(07)6382-8.
9. Jarti T, Gern JE. Role of viral infections in the development and exacerbation of asthma in children. J Allergy Clin Immunol. 2017;140:989–906. https://doi.org/10.1016/j.jaci.2017.08.003.
10. Holt PG, Sly PD. Viral infections and atopy in asthma pathogenesis: new rationales for asthma prevention and treatment. Nat Med. 2012;18:726–35. https://doi.org/10.1038/nm.2768.
11. Cusick MF, Libbey JE, Fujinami RS. Molecular mimicry as a mechanism of autoimmune disease. Clin Rev Allergy Immunol. 2012;42:102–11. https://doi.org/10.1007/s12016-011-8294-7.
12. Netea MG, Quintin J, van der Meer JW. Trained immunity: a memory for innate host defense. Cell Host Microbe. 2011;9:355–61. https://doi.org/10.1016/j.chom.2011.04.006.
13. Goodridge HS, Ahmed SS, Curtis N, Kollmann TR, Levy O, Netea MG, et al. Harnessing the beneficial heterologous effects of vaccination. Nat Rev Immunol. 2016;16:392–400. https://doi.org/10.1038/nri.2016.43.
14. Martin SF. Adaptation in the innate immune system and heterologous innate immunity. Cell Mol Life Sci. 2014;71:4115–30. https://doi.org/10.1007/s00018-014-1676-2.
15. Corti D, Bianchi S, Vanzetta F, Minola A, Perez L, Agatic G, et al. Cross-neutralization of four paramyxoviruses by a human monoclonal antibody. Nature. 2013;501:439–43. https://doi.org/10.1038/nature12442.
16. D’Orsogna L, van den Heuvel H, van Kooten C, Heidt S, Claas FJH. Infectious pathogens may trigger specific allo-HLA reactivity via multiple mechanisms. Immunogenetics. 2017;69:631–41. https://doi.org/10.1007/s00122-017-0100-6.
17. Guo H, Topham DJ. Multiple distinct forms of CD8+ T cell cross-reactivity and specificities revealed after 2009 H1N1 influenza virus infection in mice. PLoS ONE. 2012;7:1–11. https://doi.org/10.1371/journal.pone.0046166.
18. Sridhar S, Begom S, Bermingham A, Hoschler K, Adamson W, Carman W, et al. Cellular immune correlates of protection against symptomatic pandemic influenza. Nat Med. 2013;19:1305–12. https://doi.org/10.1038/nm.3350.
19. Steinke JW, Liu L, Turner RB, Braciale TJ, Borish L. Immune surveillance by rhinovirus-specific circulating CD4+ and CD8+ T lymphocytes. PLoS ONE. 2015;10:e0115271. https://doi.org/10.1371/journal.pone.0115271.
20. Wilkinson TM, Li CK, Chui CS, Huang AK, Perkins M, Liebner JC, et al. Preexisting influenza-specific CD4+ T cells correlate with disease protection against influenza challenge in humans. Nat Med. 2012;18:276–82. https://doi.org/10.1038/nm.2612.
21. Acieroni PM, Newton DA, Brown EA, Maes L, Baatz JE, Gattoni-Celli S, et al. Cross-reactivity between HLA-A2-restricted FLU-M1:58–66 and HIV p17 GAG:77–85 epitopes in HIV-infected and uninfected individuals. J Transl Med. 2003;1(13)https://doi.org/10.1186/1479-5876-1-3.
22. Wedemeyer H, Mizukoshi E, Davis AR, Bennink JR, Rehermann B. Cross-reactivity between hepatitis C virus and Influenza A virus determinant-specific cytotoxic T cells. J Virol. 2001;75:11392–400. https://doi.org/10.1128/JVI.75.23.11392.

23. Su L, Kidd B, Han A, Kotzin J, Davis M. Virus-specific CD4+ memory-phenotype T cells are abundant in unexposed adults. Immunity. 2013;38:373–83.

24. Vujanovic L, Shi J, Kirkwood JM, Storkus WJ, Butterfield LH. Molecular mimicry of MAGE-A6 and mycoplasma penetrans HF-2 epitopes in the induction of antitumor CD8+ T-cell responses. Oncoimmunology. 2014;3:e954501. https://doi.org/10.4161/21624011.2014.954501.

25. Johnson LR, Weizman O-E, Rapp M, Way SS, Sun JC. Epitope-specific vaccination limits clonal expansion of heterosexual naive T cells during viral challenge. Cell Rep. 2016;17:636–44. https://doi.org/10.1016/j.celrep.2016.09.019.

26. Oberle SG, Hanna-El-Daher L, Chennupati V, Enouz S, Scherer S, Prlic M, Zehn D. A minimum epitope overlap between infections strongly narrows the emerging T cell repertoire. Cell Rep. 2016;17:627–35. https://doi.org/10.1016/j.celrep.2016.09.072.

27. Urbani S, Amadei B, Fisicaro P, Pilli M, Missale G, Bertoletti A, Ferrari C. Heterologous T cell immunity in severe hepatitis C virus infection. J Exp Med. 2005;201:673–80. https://doi.org/10.1084/jem.20041058.

28. Welsh RM, Che JW, Brehm MA, Selin LK. Heterologous immunity between viruses. Immunol Rev. 2010;235:244–66. https://doi.org/10.1111/j.1600-065X.2010.00897.x.

29. Wucherpfennig KW, Strominger JL. Molecular mimicry in T cell-mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein. Cell. 1995;80:695–705. https://doi.org/10.1016/0092-8674(95)90348-8.

30. Heutinck KM, Yong SL, Tonneijck L, van den Heuvel JL, Luzuriaga K, et al. Type I interferons regulate cytolytic activity of CD8+ T-cell responses. Oncoimmunology. 2014;3:e954501. https://doi.org/10.4161/21624011.2014.954501.

31. Younes S-A, Freeman ML, Mudd JC, Shive CL, Reynaldi A, Panigrahi S, et al. IL-15 promotes activation and expansion of CD8+ T cells in HIV-1 infection. J Clin Invest. 2012;126:2745–56. https://doi.org/10.1172/JCI85996.

32. Lertmemongkolchai G, Cai G, Hunter CA, Bancroft GJ. Bystander activation of CD8+ T cells contributes to the rapid production of IFN-β in response to bacterial pathogens. J Immunol. 2001;166:1097–105. https://doi.org/10.4049/jimmunol.166.2.1097.

33. Kohlmeier JE, Cookenham T, Roberts AD, Miller SC, Wood-Mason OC, Rapp M, et al. A novel vaccination strategy mediating the induction of lung-resident memory CD8 T cells confers heterosubtypic immunity against future pandemic influenza virus. J Immunol. 2016;196:2637–45. https://doi.org/10.4049/jimmunol.1501637.

34. Zens KD, Chen JK, Farber DL. Vaccine-generated lung tissue-resident memory T cells provide heterosubtypic protection to influenza infection. JCI Insight. 2016;https://doi.org/10.1172/jci.insight.85832.

35. Che JW, Selin LK, Welsh RM. Evaluation of non-reciprocal heterologous immunity between unrelated viruses. Virology. 2015;482:89–97. https://doi.org/10.1016/j.virol.2015.03.002.

36. Sewell AK. Why must T cells be cross-reactive? Nat Rev Immunol. 2012;12:669–77. https://doi.org/10.1038/nri3279.

37. Arstila TP. A direct estimate of the human T cell receptor repertoire. Science. 1999;286:558–61. https://doi.org/10.1126/science.286.5441.958.

38. Mason D. A very high level of crossreactivity is an essential feature of the T-cell receptor. Immunol Today. 1998;19:395–404. https://doi.org/10.1016/S0167-5699(98)01299-7.

39. Wooldridge L, Ekeruche-Makinde J, van den Berg HA, Skowera A, Miles JJ, Tan MP, et al. A single autoimmune T cell receptor recognizes more than a million different peptides. J Biol Chem. 2012;287:1168–77. https://doi.org/10.1074/jbc.M111.289488.

40. Kagnoff MF, Austin RK, Hubert JB, Bernardin JE, Kasarda DD. Possible role for a human adenovirus in the pathogenesis of celiac disease. J Exp Med. 1984;160(5):1544–57.

41. Nilges K, Höhn H, Pilch H, Neukirch C, Freitag K, Talbot PJ, et al. Cross-reactivity between hepatitis C virus and human T cell clones specific for myelin basic protein. J Immunol. 1997;158:298–305. https://doi.org/10.4049/jimmunol.1501637.

42. Nigrovic-Plesse S, Hemmer B, Wang GC, Monk GP, et al. Molecular basis for universal HLA-A*0201-restricted CD8+ T-cell immunity against influenza viruses. Proc Natl Acad Sci USA. 2016;113:4440–5. https://doi.org/10.1073/pnas.1603106113.

43. Clute SC, Watkin LB, Cornberg M, Naumov YN, Sullivan JL, Luzuriaga K, et al. Cross-reactive influenza virus-specific CD8+ T cells contribute to lymphoproliferation in Epstein-Barr virus-associated infectious mononucleosis. J Clin Invest. 2005;115:3602–12. https://doi.org/10.1172/jci25078.

44. Cornberg M, Clute SC, Watkin LB, Saccoccio FM, Kim S-K, Naumov YN, et al. CD8 T cell cross-reactivity networks mediate heterologous immunity in human EBV and murine vaccinia virus infections. J Immunol. 2010;184:2825–38. https://doi.org/10.4049/jimmunol.0902168.

45. Markovic-Plese S, Hemmer B, Zhou Y, Simon R, Pinilla C, Martin R. High level of cross-reactivity in influenza virus hemagglutinin-specific CD4+ T-cell response: implications for the initiation of autoimmune response in multiple sclerosis. J Neuroimmunol. 2005;169:31–8. https://doi.org/10.1016/j.jneuroim.2005.07.014.
51. Hucklehoven AG, Etschel JK, Bergmann S, Zitzelsberger K, Mueller-Schmucker SM, Harrer EG, Harrer T. Cross-reactivity between influenza matrix- and HIV-1 P17-specific CTL-A large cohort study. J Acquir Immune Defic Syndr. 2015;69:528–35. https://doi.org/10.1097/QAI.0000000000000657.

52. Ekeruche-Makinde J, Miles JJ, van den Berg HA, Skowera A, Cole DK, Dolton G, et al. Peptide length determines the outcome of TCR/peptide-MHCII engagement. Blood. 2013;121:1112–23. https://doi.org/10.1182/blood-2012-06-437202.

53. Adams JJ, Narayanan S, Birnbaum ME, Sidhu SS, Blevins SJ, Gee MH, et al. Structural interplay between germline interactions and adaptive recognition determines the bandwidth of TCR-peptide-MHCII cross-reactivity. Nat Immunol. 2016;17:87–94. https://doi.org/10.1038/ni.3310.

54. van Regenmortel MHV. Specificity, polyspecificity, and heterospecificity of antibody-antigen recognition. J Mol Recognit. 2014;27:627–39. https://doi.org/10.1002/jmr.2394.

55. Ringelum Jv, Nielsen M, Pudjkaer SB, Lund O. Structural analysis of B-cell epitopes in antibody: protein complexes. Mol Immunol. 2013;53:24–34. https://doi.org/10.1016/j.molimm.2012.06.001.

56. Sela-Culang I, Kunik V, Ofran Y. The structural basis of antibody-antigen recognition. Front Immunol. 2013;4:302. https://doi.org/10.3389/fimmu.2013.00302.

57. Channappanavar R, Fettk C, Zhao J, Meyerholz DK, Perlman S. Virus-specific memory CD8 T cells provide substantial protection from lethal severe acute respiratory syndrome coronavirus infection. J Virol. 2014;88:11034–44. https://doi.org/10.1128/JVI.01505-14.

58. Liu WJ, Zhao M, Liu K, Xu K, Wong G, Tan W, Gao GE. T-cell immunity of SARSCoV: implications for vaccine development against MERS-CoV. Antiviral Res. 2017;137:82–92. https://doi.org/10.1016/j.antiviral.2016.11.006.

59. Tai W, Wang Y, Fett CA, Zhao G, Li F, Perlman S, et al. Recombinant receptor-binding domains of multiple middle east respiratory syndrome coronaviruses (MERS-CoVs) induce cross-neutralizing antibodies against divergent human and camel MERS-CoVs and antibody escape mutants. J Virol. 2017;https://doi.org/10.1128/JVI.01651-16.

60. Zhao J, Zhao J, Mangalam AK, Channappanavar R, Fett C, Meyerholz DK, et al. Airway memory CD4(+) T cells mediate protective immunity against emerging respiratory coronaviruses. Immunology. 2016;144:1379–91. https://doi.org/10.1111/ijim.12606.

61. Tu W, Mao H, Zheng J, Liu Y, Chiu SS, Qin G, et al. Cytotoxic T lymphocytes established by seasonal human influenza cross-react against 2009 pandemic H1N1 influenza virus. J Virol. 2010;84:6527–35. https://doi.org/10.1128/JVI.00519-10.

62. Li J, Árevolo MT, Chen Y, Chen S, Zeng M. T-cell-mediated cross-strain protective immunity elicited by prime-boost vaccination with a live attenuated influenza vaccine. Int J Infect Dis. 2014;27:37–43. https://doi.org/10.1016/j.ijid.2014.05.050.

63. Mohan KGI, Zhou F, Brokstad KA, Sridhar S, Cox RJ. Boosting of cross-reactive and protection-associated T cells in children after live attenuated influenza vaccination. J Infect Dis. 2017;215:1527–35. https://doi.org/10.1093/infdis/jix165.

64. Magini D, Giovanni C, Mangiavacchi S, Maccari S, Cecchi R, Ulmer JB, et al. Self-amplifying mRNA vaccines expressing multiple conserved influenza antigens confer protection against homologous and heterosubtypic viral challenge. PLoS ONE. 2016;11:e161193. https://doi.org/10.1371/journal.pone.0161193.

65. Chua BY, Wong CY, Mifsud EJ, Edendburgh KM, Sekiya T, Tan ACL, et al. Inactivated influenza vaccine that provides rapid, innate-immune- system-mediated protection and subsequent long-term adaptive immunity. MBio. 2015;6:1–11. https://doi.org/10.1128/mBio.01024-15.

66. Krammer F, Palese P. Influenza virus hemagglutinin stalk-based antibodies and vaccines. Curr Opin Virol. 2013;3:521–30. https://doi.org/10.1016/j.coviro.2013.07.007.

67. Ellebedy AH, Krammer F, Li G-M, Miller MS, Chiu C, Wrammert J, et al. Induction of broadly cross-reactive antibody responses to the influenza HA stem region following H5N1 vaccination in humans. Proc Natl Acad Sci USA. 2014;111:13133–8. https://doi.org/10.1073/pnas.1414070111.

68. Krammer F. Novel universal influenza virus vaccine approaches. Curr Opin Virol. 2016;17:95–103. https://doi.org/10.1016/j.coviro.2016.02.002.

69. Carter DM, Darby CA, Lefoley BC, Crevar CJ, Alefantis T, Oomen R, et al. Design and characterization of a computationally optimized broadly reactive hemagglutinin vaccine for H1N1 influenza viruses. J Virol. 2016;90:4720–34. https://doi.org/10.1128/JVI.03152-15.

70. Deng L, Cho KJ, Fiers W, Saelens X. M2e-based universal influenza A vaccines. Vaccines (Basel). 2015;3:105–36. https://doi.org/10.3390/vaccines3010105.

71. Eliasson DG, Omokanye A, Schön K, Wenzel UA, Bernasconi V, Bemark M, et al. M2e-tetramer-specific memory CD4 T cells are broadly protective against influenza infection. Mucosal Immunol. 2017;https://doi.org/10.1038/mi.2017.14.

72. Schotsaert M, Ysenbaert T, Smet A, Schepens B, Vander-schaeghe D, Stegalkina S, et al. Long-lasting cross-protection against influenza A by neuraminidase and M2e-based immunization strategies. Sci Rep. 2016;https://doi.org/10.1038/srep24402.

73. Ramos EL, Mitcham JL, Koller TD, Bonavia A, Usner DW, Balaratnam G, et al. Broadly reactive anti-respiratory syncytial virus G antibodies from exposed individuals effectively inhibit infection of primary airway epithelial cells. J Virol. 2017;https://doi.org/10.1128/JVI.02357-16.

74. Graham BS. Vaccines against respiratory syncytial virus: the time has finally come. Vaccine. 2016;34:3535–41. https://doi.org/10.1016/j.vaccine.2016.04.083.

75. Cortjens B, Yasuda E, Yu X, Wagner K, Claassen YB, Bakker AQ, et al. Broadly reactive anti-respiratory syncytial virus G antibodies from exposed individuals effectively inhibit infection of primary airway epithelial cells. J Virol. 2017;https://doi.org/10.1128/JVI.02357-16.

76. Lee J-Y, Chang J. Universal vaccine against respiratory syncytial virus A and B subtypes. PLoS ONE. 2017;12:e0175384. https://doi.org/10.1371/journal.pone.0175384.

77. Taylor G, Thom M, Capone S, Pierantoni A, Guzman E, Herbert R, et al. Efficacy of a virus-vectored vaccine against human metapneumovirus and respiratory syncytial virus. J Infect Dis. 2015;211:1038–44. https://doi.org/10.1093/infdis/jiu539.

78. Schotsaert M, Ysenbaert T, Smet A, Schepens B, Vanderschaeghe D, Stegalkina S, et al. Long-lasting cross-protection against influenza A by neuraminidase and M2e-based immunization strategies. Sci Rep. 2016; https://doi.org/10.1038/srep24402.
80. Muehling LM, Mai DT, Kwok WW, Heymann PW, Pomes A, Woodfolk JA. Circulating memory CD4+ T cells target conserved epitopes of rhinovirus capsid proteins and respond rapidly to experimental infection in humans. J Immunol. 2016;197:3214–24. https://doi.org/10.4049/jimmunol.1600663.

81. Iwasaki J, Smith W-A, Thomas WR, Hales BJ. Species-specific and cross-reactive IgG1 antibody binding to viral capsid protein 1 (VP1) antigens of human rhinovirus species A, B and C. PLoS ONE. 2013;8:e70552. https://doi.org/10.1371/journal.pone.0070552.

82. Niespodziana K, Napor A, Cabauatan C, Focke-Tejkl M, Keller W, Niederberger V, et al. Misdirected antibody responses against an N-terminal epitope on human rhinovirus VP1 as explanation for recurrent RV infections. Faseb J. 2012;26:1001–8. https://doi.org/10.1096/fj.11-193557.

83. Aslan N, Watkin LB, Gil A, Mishra R, Clark FG, Welsh RM, et al. Severity of acute infectious mononucleosis correlates with cross-reactive influenza CD8 T-cell receptor repertoires. MBio. 2017; https://doi.org/10.1128/mBio.01841-17.

84. Odumade OA, Knight JA, Schmeling DO, Masopust D, Zhang S, Bakshe R, Suneetha PV, Fytiti P, Antunes DA, Vieira K-Y, Luo Z-W, Montgomery HM, Antrim AM, Fauci AS, et al. Cross-reactive influenza CD8+ T-cell reactivity in individuals infected with hepatitis C virus. J Virol. 2015;89:8304–17. https://doi.org/10.1128/JVI.00539-15.

85. Watkin LB, Mishra R, Gil A, Aslan N, Gherzi D, Luzuriaga K, Selin LK. Unique influenza A cross-reactive memory C D 8 T-cell receptor repertoire has a potential to protect against EBV seroconversion. J Allergy Clin Immunol. 2017;140:1206–10. https://doi.org/10.1016/j.jaci.2017.05.037.

86. Price CS, Bakshi RK, Suneetha PV, Fytiti P, Antunes DA, Vieira GE, et al. Frequency, private specificity, and cross-reactivity of preexisting hepatitis C virus (HCV)-specific CD8+ T cells in HCV-seronegative individuals: implications for vaccine responses. J Virol. 2015;89:8304–17. https://doi.org/10.1128/JVI.00539-15.

87. Kasprzowicz V, Ward SM, Turner A, Grammaticos A, Nolan BE, Lewis-ximenez L, et al. Defining the directionality and quality of influenza virus-specific CD8+ T-cell cross-reactivity in individuals infected with hepatitis C virus. J Clin Invest. 2008;118:1143–53. https://doi.org/10.1172/JCI33082DS1.

88. Ertl HC. Viral vectors as vaccine carriers. Curr Opin Virol. 2016;17:1–8. https://doi.org/10.1016/j.coviro.2016.06.001.

89. Kotterman MA, Chalberg TW, Schaffer DV. Viral vectors for gene therapy: translational and clinical outlook. Annu Rev Biomed Eng. 2015;17:63–89. https://doi.org/10.1146/annurev-bioeng-071813-104938.

90. Singh S, Vedi S, Samrat SK, Li W, Kumar R, Agrawal B. Heterologous immunity between adenoviruses and hepatitis C virus: a new paradigm in HCV immunity and vaccines. PLoS ONE. 2016;11:1–23. https://doi.org/10.1371/journal.pone.0146404.

91. Frahm N, DeCamp AC, Friedrich DP, Carter DK, Defawe OD, Kublin JG, et al. Human adenovirus-specific T cells modulate HIV-specific T cell responses to an Ad5-vecotreded HIV-1 vaccine. J Clin Invest. 2012;122:359–67. https://doi.org/10.1172/JCI60202.

92. Pennington SH, Thompson AL, Wright AKA, Ferreira DM, Jambo KC, Wright AD, et al. Oral typhoid vaccination with live-attenuated Salmonella typhi strain Ty21a generates Ty21a-responsive and heterologous influenza virus–responsive CD+ and CD8+ T cells at the human intestinal mucosa. J Infect Dis. 2016;213:1809–19. https://doi.org/10.1093/infdis/jiw030.

93. Tenembaum S, Chitnis T, Ness J, Hahn JS. Acute disseminated encephalomyelitis. Neurology. 2007;68(16 Suppl 2):S23–S36.

94. Karussis D, Petrou P. The spectrum of post-vaccination inflammatory CNS demyelinating syndromes. Autoimmun Rev. 2014;13:215–24. https://doi.org/10.1016/j.autrev.2013.10.003.

95. Ravagna S, Ceroni M, Moglia A, Todeschini A, Marchioni E. Post-infectious and post-vaccinal acute disseminated encephalomyelitis occurring in the same patients. J Neurol. 2004;251:1147–50. https://doi.org/10.1007/s00415-004-0498-9.

96. Athauda D, Andrews TC, Holmes PA, Howard RS. Multiphasic acute disseminated encephalomyelitis (ADEM) following influenza type A (swine specific H1N1). J Neurol. 2012;259:775–8. https://doi.org/10.1007/s00415-011-6258-8.

97. Au WY, Lie AKW, Cheung RTE, Cheng PW, Ooi CGC, Vujenc K-Y, Kwong Y-L. Acute disseminated encephalomyelitis after para-influenza infection post bone marrow transplantation. Leuk Lymphoma. 2002;43:455–7. https://doi.org/10.1080/10428190290006350.

98. Sellers SA, Hagan RS, Hayden FG, Fischer WA. The hidden burden of influenza: a review of the extra-pulmonary complications of influenza infection. Influenza Other Respir Viruses. 2017;11:372–93. https://doi.org/10.1016/j.infe.2017.07.12470.

99. Blackmore S, Hernandez J, Juda M, Ryder E, Freund GG, Johnson RW, Steelman AJ. Influenza infection triggers disease in a genetic model of experimental autoimmune encephalomyelitis. Proc Natl Acad Sci USA. 2017;114:E6107–E16. https://doi.org/10.1073/pnas.1620415114.

100. Chen Q, Liu Y, Lu A, Ni K, Xiang Z, Wen K, Tu W. Influenza virus infection exacerbates experimental autoimmune encephalomyelitis disease by promoting type I T cells infiltration into central nervous system. J Autoimmun. 2017;77:1–10. https://doi.org/10.1016/j.jaut.2016.10.006.

101. Sriram S, Steiner I. Experimental allergic encephalomyelitis: a misleading model of multiple sclerosis. Ann Neurol. 2005;58:939–49.http://doi.org/10.1002/ana.20743.

102. Poli-Koppe A, Burchett SK, Thiele EA, Haller DA. Myelin basic protein reactive Th2 T cells are found in acute disseminated encephalomyelitis. J Neuroimmunol. 1998;91:19–27. https://doi.org/10.1016/S0165-5728(98)00012-5.

103. Hennes E-M, Baumann M, Schanda K, Anlar B, Bajer-Kornek B, Blaschek A, et al. Prognostic relevance of MOG antibodies in children with an acquired demyelinating syndrome. Neurology. 2017;89:900–8. https://doi.org/10.1212/WMN.0000000000014312.

104. Boucher A, Desforges M, Duquette P, Talbot P. Long-term human coronavirus-myelin cross-reactive T-cell clones derived from multiple sclerosis patients. Clin Immunol. 2007;123:258–67. https://doi.org/10.1016/j.clim.2007.02.002.

105. Peschl P, Bradl M, Höfßberger R, Berger T, Reindl M. Myelin oligodendrocyte glycoprotein: deciphering a target in inflammatory demyelinating diseases. Front Immunol. 2017;8:529. https://doi.org/10.3389/fimmu.2017.00529.

106. Lehmann HC, Hartung H-P, Kieseier BC, Hughes RA, Guillin-Barré syndrome after exposure to influenza virus. Lancet Infect Dis. 2010;10:643–51.

107. Martín Arias LH, Sanz R, Sainz M, Treceno C, Carvajal A, Guillin-Barré syndrome and influenza vaccines: a meta-analysis. Vaccine. 2015;33:3773–8. https://doi.org/10.1016/j.vaccine.2015.05.013.
108. Nachamkin I, Shaddy SV, Moran AP, Cox N, Fitzgerald C, Ung H, et al. Anti-ganglioside antibody induction by swine (A/NJ/1976/H1N1) and other influenza vaccines: insights into vaccine-associated Guillain-Barré syndrome. J Infect Dis. 2008;198:226–33. https://doi.org/10.1086/589624.

109. Partinen M, Kornum BR, Plazzi G, Jennum F, Jüllkunen I, Vaarala O. Narcolepsy as an autoimmune disease: the role of H1N1 infection and vaccination. Lancet Neurol. 2014;13:600–13. https://doi.org/10.1016/S1474-4422(14)70075-4.

110. Han F, Lin W, Warby SC, Faraco J, Dong SX, et al. Narcolepsy onset is seasonal and increased following the 2009 H1N1 pandemic in China. Ann Neurol. 2011;70:410–7. https://doi.org/10.1002/ana.22587.

111. Ahmed SS, Volkmuth W, Duca J, Corti L, Pallaoro M, Pezzicoli A, et al. Antibodies to influenza nucleoprotein cross-react with human hypoxerin receptor Z. Sci Transl Med. 2015;7:294ra105. https://doi.org/10.1126/scitranslmed.aab2354.

112. Caforio ALP, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, et al. Current state of knowledge on autoimmunity and vaccination. Curr Opin Rheumatol. 2013;25:480–7. https://doi.org/10.1097/BOR.0b013e32836200d2.

113. Igoe A, Scofield RH. Autoimmunity and infection in Sjögren's syndrome: an update. J Inflamm Res. 2017;10:97–105. https://doi.org/10.2147/JIR.S137024.

114. Singh N, Cohen PL. The T cell in Sjögren's syndrome: force majeure, not spectateur. J Autoimmun. 2012;39:229–33. https://doi.org/10.1016/j.jaut.2012.05.019.

115. Lennard-Jones EJ, Toshniwal P, Raine CS, Wright G, Doherty PM. Infection with the pandemrix vaccination campaign in Sweden derived from human adeno virus 12 which resembles a sequence of A-gliadin in patients with celiac disease. Gut. 1987;31:668–73.

116. Prüss H, Finke C, Höltje M, Hofmann J, Klingbeil C, Probst C, et al. Peptide sharing between simplexencephalitis. Ann Neurol. 2012;72:902–11. https://doi.org/10.1002/ana.23689.

117. Kupfer SS, Jabri B. Pathophysiology of celiac disease. Gastrointestinal Endosc Clin N Am. 2012;22:839–60. https://doi.org/10.1016/j.gie.2012.07.003.

118. Gangaplara A, Massilamany C, Brown DM, Delhon G, Pattnaik AK, Chapman N, et al. Coxsackievirus B3 infection leads to the generation of cardiac myosin heavy chain-α reactive CD4 T cells in A/J mice. Clin Immunol. 2012;144:237–49. https://doi.org/10.1016/j.clim.2012.07.003.

119. Unsworth DJ, Austin RK. Evidence for the role of a human adenovirus 12 which resembles a sequence of A-gliadin in patients with celiac disease. Am J Epidemiol. 1987;28:995–1001.

120. Früiss H, Finke C, Höltje M, Hoffmann J, Klengbeil C, Probst C, et al. α-N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. Ann Neurol. 2012;72:902–11. https://doi.org/10.1002/ana.23689.

121. Berger B, Pytklik M, Hottenrott T, Stich O. Absent anti-N-methyl-D-aspartate receptor NR1a antibodies in herpes simplex encephalitis. Ann Neurol. 2012;72:1272–6. https://doi.org/10.1002/ana.22587.

122. Wheatland R. Molecular mimicry of ACTH in SARS—implications for corticosteroid treatment and prophylaxis. Med Hypotheses. 2004;63:855–62. https://doi.org/10.1016/j.mehy.2004.04.009.

123. Beyerlein A, Donnachie E, Ziegler A-G. Infections in early life and development of celiac disease. Am J Epidemiol. 2017; https://doi.org/10.1093/aje/kwx190.

124. Kagnoff MF, Paterson YJ, Kumar PJ, Kasarda DD, Carbone FR, Unsworth DJ, Austin BK. Evidence for the role of a human intestinal adenovirus in the pathogenesis of celiac disease. Gut. 1987;28:995–1001.

125. Mantzaris GJ, Karagiannis JA, Priddle JD, Jewell DP. Cellular hypersensitivity to a synthetic dodecapeptide derived from human adenovirus 12 which resembles a sequence of A-gliadin in patients with celiac disease. Gut. 1990;31:668–73.

126. Kupfer SS, Jabri B. Pathophysiology of celiac disease. Gastrointestinal Endosc Clin N Am. 2012;22:839–60. https://doi.org/10.1016/j.gie.2012.07.003.

127. Grimsmo SY, Vagenakis AG, Wyss LM, Ziegler AG. Infections in early life and development of celiac disease. J Autoimmun. 2014;72:1272–6. https://doi.org/10.1002/ana.22587.

128. Massilamany C, Gangaplara A, Steffen D, Reddy J. Identification of novel mimicry epitopes for cardiac myosin heavy chain-α that induce autoimmune myocarditis in A/J mice. Cell Immunol. 2011;271:438–49. https://doi.org/10.1016/j.cellimm.2011.08.013.

129. Gangaplara A, Massilamany C, Brown DM, Delhon G, Pattnaik AK, Chapman N, et al. Coxsackievirus B3 infection leads to the generation of cardiac myosin heavy chain-α reactive CD4 T cells in A/J mice. Clin Immunol. 2012;144:237–49. https://doi.org/10.1016/j.clim.2012.07.003.

130. Root-Bernstein R. Rethinking molecular mimicry in rheumatic heart disease and autoimmune myocarditis: laminin, collagen IV, CAR, and B1AR as initial targets of disease. Front Pediatr. 2014;2:65. https://doi.org/10.3389/fped.2014.00065.

131. Nachamkin I, Shaddy SV, Moran AP, Cox N, Fitzgerald C, Ung H, et al. Anti-ganglioside antibody induction by swine (A/NJ/1976/H1N1) and other influenza vaccines: insights into vaccine-associated Guillain-Barré syndrome. J Infect Dis. 2008;198:226–33. https://doi.org/10.1086/589624.
137. Op de Beeck A, Eizirik DL. Viral infections in type 1 diabetes mellitus—why the β cells? Nat Rev Endocrinol. 2016;12:263–73. https://doi.org/10.1038/nrendo.2016.30.

138. Hiemstra HS, Schloot NC, van Rood JJ, Willemen SJM, Franken KL, de Vries RRP et al. Cytomegalovirus in autoimmunity: T cell crossreactivity to viral antigen and autoantigen glutamic acid decarboxylase. Proc Natl Acad Sci USA. 2001;98:3898–91.

139. Honeyman MC, Stone NL, Falk BA, Nepom G, Harrison LC. Evidence for molecular mimicry between human T cell epitopes in rotavirus and pancreatic islet autoantigens. J Immunol. 2010;184:2204–10. https://doi.org/10.4049/jimmunol.0900709.

140. Qi Z, Hu H, Wang Z, Wang G, Li Y, Zhao X, et al. Antibodies against H1N1 influenza virus cross-react with α-cells of pancreatic islets. J Diabetes Investig. 2017; https://doi.org/10.1111/jdi.12690.

141. Thorel F, Népote V, Avril I, Kohno K, Desgraz R, Chera S, Herrera PL. Conversion of adult pancreatic α-cells to β-cells after extreme β-cell loss. Nature. 2010;464:1149–54. https://doi.org/10.1038/nature08894.

142. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy. 2004;59:469–78. https://doi.org/10.1111/j.1398-9995.2004.00526.x.

143. Lützell J, Pawankar R, Wallace DV, Akdis CA, Rosenwasser LJ, Weber RW, et al. We call for iCAALL: International Collaboration in Asthma, Allergy and Immunology. World Allergy Organ J. 2012;5:39–40. https://doi.org/10.1097/ WOX.0b013e3182504245.

144. Papadopoulos NG, Christodoulou I, Rohde G, Agache I, Almqvist C, Bruno A, et al. Viruses and bacteria in acute asthma exacerbations—a GA² LEN-DARE systematic review. Allergy. 2011;66:458–68. https://doi.org/10.1111/j.1398-9995.2010.02505.x.

145. Lukkarinen M, Koistinen A, Turunen R, Lehtinen P, Vuorenen T, Jartti T. Rhinovirus-induced first wheezing episode predicts atopic but not nonatopic asthma at school age. J Allergy Clin Immunol. 2017;140:988–95. https://doi.org/10.1016/j.jaci.2016.12.991.

146. Jackson DJ, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Pappas TE, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. Am J Respir Crit Care Med. 2008;178:667–72. https://doi.org/10.1164/rccm.200802-309OC.

147. Strachan DP. Hay fever, hygiene, and household size. BMJ. 1989;299:1259–60. https://doi.org/10.1136/bmj.299.6710.1259.

148. Garn H, Renz H. Epidemiological and immunological evidence for the hygiene hypothesis. Immunobiology. 2007;212:441–52. https://doi.org/10.1016/j.imbio.2007.03.006.

149. Machiels B, Dourcy M, Xiao X, Javala J, Mesnil C, Sabatel C, et al. A gammaherpesvirus provides protection against allergic asthma by inducing the replacement of resident alveolar macrophages with regulatory monocytes. Nat Immunol. 2017;18:1310–20.

150. Chang Y-J, Kim HY, Albacker LA, Lee HH, Baumgarth N, Akira S, et al. Influenza infection in suckling mice expands an NKT cell subset that protects against airway hyperreactivity. J Clin Invest. 2011;121:57–69. https://doi.org/10.1172/JCI44845.

151. Conrad ML, Ferstl R, Teich R, Brand S, Blümer N, Yildirim AO, et al. Maternal TLR signaling is required for prenatal asthma protection by the nonpathogenic microbe acinetobacter lwoffii F78. J Exp Med. 2009;206:2869–77. https://doi.org/10.1084/jem.20090845.

152. Wohlleben G, Muller J, Tatsch U, Hambrecht C, Herz U, Renz H, et al. Influenza A virus infection inhibits the efficient recruitment of Th2 cells into the airways and the development of airway eosinophilia. J Immunol. 2003;170:4601–11. https://doi.org/10.4049/jimmunol.170.9.4601.

153. Skevaki C, Hudemann C, Matrosovich M, Möbs C, Paul S, Wachtendorf A, et al. Influenza-derived peptides cross-react with allergens and provide asthma protection. J Allergy Clin Immunol. 2017; https://doi.org/10.1016/j.jaci.2017.07.056.

154. Bien CG, Bauer J. Autoimmune epilepsies. Neurotherapeutics. 2014;11:311–8. https://doi.org/10.1007/s13311-014-0264-3.

155. Mustalahti K, Catassi C, Reunanen A, Fabiani E, Heier M, McMillan S, et al. The prevalence of celiac disease in Europe: results of a centralized, international mass screening project. Ann Med. 2010;42:587–95. https://doi.org/10.3109/07853890.2010.505931.

156. Lerner A, Arleevskaya M, Schmiedl A, Matthias T. Microbes and viruses are bugging the gut in celiac disease. Are they friends or foes? Front Microbiol. 2017;8:1392. https://doi.org/10.3389/fmicb.2017.01392.