Vaccination with bovine, chick, yeast antigens synthesizes cross-reactive antibodies targeting human acetylcholine receptor and MuSK protein to cause Myasthenia Gravis: Confirmed by natural experiment (VAERS data), bioinformatics, case reports, animal experiments and titer study

Vinu Arumugham
Sep 2019
vinucubeacc@gmail.com

Abstract

Myasthenia Gravis (MG) is a neuromuscular junction disorder. It is caused by antibodies directed against the acetylcholine receptor (AchR) or Muscle-Specific Kinase (MuSK) protein. 45 years ago, researchers discovered that immunizing rabbits with AchR from an electric eel, resulted in an MG like disease. Immunizing with the AchR protein is now the usual method used to induce experimental autoimmune MG (EAMG).

Development of MG is reported following the administration of many vaccines. Most cases occur following administration of the influenza vaccines per the Vaccine Adverse Event Reporting System (VAERS). A study found 20-81.2% AchR antibody level increase in 2 out of 31 patients following egg derived influenza vaccine administration and most of whom were on immunosuppressive treatment. Most influenza vaccines are manufactured using embryonated chicken eggs and contain residual egg proteins. Embryonated chicken eggs contain the chick AchR protein. We show that the chick AchR protein sequence differ from human AchR by just one or two amino acid residues. Thus they are ideally suited to activate human low affinity self reactive (LASR) T cells. These human LASR T cells that recognize human AchR with low affinity can escape the thymus due to positive selection. Such T cells with T cell receptors (TCR) that bind with high affinity to chick AchR can be activated by injected chick AchR proteins.
These activated T cells interact with B cells and initiate antibody production directed against chick AchR. These antibodies cross react with human AchR to cause MG.

Vaccines contain numerous animal proteins. Many of those AchR proteins are also similar to human AchR. So as above, many of these vaccines cause MG.

Similar mechanism is involved in Graves' disease (GD). Yeast (*Saccharomyces cerevisiae*) is used to produce recombinant Hepatitis B vaccine (HBV), Human Papillomavirus vaccine (HPV) and injectable insulin products. We show significant protein sequence homology between GD autoepitopes, animal proteins and *S. cerevisiae* proteins. Humoral immune response directed against *S. cerevisiae* occurs following HBV, HPV administration and prolonged injectable insulin usage as in type 1 diabetes. Thus leading to the development of GD and numerous other autoimmune disorders.

Important findings: Animal protein containing vaccines cause autoimmune diseases even when the vaccine does not contain an adjuvant. Adjuvanted vaccines only make the problem worse. Vaccines interact to cause autoimmune diseases. Post-marketing vaccine safety surveillance systems are an abject failure.

Introduction

Myasthenia Gravis (MG) is a neuromuscular junction disorder. It is caused by antibodies directed against the acetylcholine receptor (AchR) or Muscle-Specific Kinase (MuSK) protein. 45 years ago, researchers discovered that immunizing rabbits with AchR from an electric eel, resulted in an MG like disease (1). Immunizing mice with the AchR protein derived from Torpedo rays is a common method used to induce experimental autoimmune MG (EAMG) (2). Both complete Freund adjuvant (CFA) and aluminum hydroxide adjuvant have been used along with AchR protein to induce EAMG (2). Aluminum hydroxide adjuvant produces milder disease compared to CFA. As a general case, we have autoimmunity as a result of immunization with homologous xenogeneic antigens, as previously described (3).

Development of MG is reported following the administration of many vaccines. (4) Most cases occur following administration of the influenza vaccines per the Vaccine Adverse Event Reporting System (VAERS). VAERS shows 497 cases of myasthenia gravis and myasthenic syndrome following influenza vaccine administration. When muscle weakness reports are included, there are more than 6000 cases. Tackenberg et al (5). report 20-81.2% AchR antibody titer increase in 2 out of 31 patients following chicken egg derived influenza vaccine administration. Most of the patients were on immunosuppressive treatment. Most influenza vaccines are manufactured using embryonated chicken eggs and contain residual egg proteins. (6) Embryonated chicken eggs contain AchR and therefore the vaccines contain residual chick AchR protein (7–9). Here we will use protein sequence analysis to compare autoepitopes involved in MG with homologous chick epitopes. If the chick and human protein match 100 %, it is unlikely to result in autoimmune disorders. This is because the immune system has strong tolerance for self antigens. However, if the autoepitopes differ slightly from chick epitopes (and they do, as we show), the immune system can be sensitized.

Vaccines contain numerous animal proteins. Many of those AchR and MuSK related proteins are also similar to human self proteins. So as above, many of these vaccines cause MG.

Similar argument applies to Graves' disease (GD). Yeast (*Saccharomyces cerevisiae*) is used to produce recombinant Hepatitis B vaccine (HBV), Human Papillomavirus vaccine (HPV) and injectable insulin products. We show significant protein sequence homology between GD epitopes, animal and S. cerevisiae proteins. Humoral immune response directed against S. cerevisiae occur following HBV, HPV administration and prolonged injectable insulin usage as in type 1 diabetes (T1D) (10). Thus leading to the development of GD and numerous other autoimmune disorders.

Methods

Protein sequences were obtained from Uniprot (11). BLASTP (12) was used to perform protein sequence analysis. The data from the US Vaccine Adverse Events Reporting System (VAERS) was obtained using the Centers for Disease Control (CDC) WONDER system (13).

Results

Using BLASTP we compare human AchR epitopes against equivalent animal peptides. The results of BLASTP analysis comparing 32 MG related autoepitopes against vaccine antigens, are shown in Table 1. These epitopes were identified by Vaughan et al. (14) 19 of 32 epitopes show a single amino acid

residue change. 8 of 32 show an amino acid residue alteration at two positions. 6 of 32 show 3 or more amino acid residue alterations. 9 of 32 autoepitopes show most homology to chick AchR peptides. 6 of 32 to guinea pig, 8 of 32 to bovine and 7 of 32 to porcine peptides.

Table 1

MG epitopes (14)	Vaccine antigen organism of origin	Common name	Example vaccines containing the antigen	BLASTP Match Score
STHVMPNWVRKVFIDTIP STHVMP**E**WVRKVFIDTIP	Bos taurus,Sus scrofa, Cavia porcellus	Cow,Pig, Guinea pig	DTaP/TdaP, Zostavax, Varivax	60.9
STHVMPNWVRKVFIDTIP STH**T**MP**P**WVRK**I**FIDTIP	Gallus gallus	Chick	MMR, MMRV, TBE, Influenza	52.8
IPNIMFFSTMKRPSREKQ IPNIMFFSTMKRPSR**D**KQ	Cavia porcellus	Guinea pig	Varivax	62.1
AIVKFTKVLLQYTGHITWTP AIVKFTKVLL**D**YTGHITWTP	Bos taurus	Cow	DTaP/TdaP, MMR,MMRV, IPV, Varivax	64.7
QIVTTNVRLKQQWVDYNLKW QIVTTNVRLKQQWVD**H**NLKW	Cavia porcellus	Guinea pig	Varivax	66.8
QIVTTNVRLKQQWVDYNLKW QIVTTNVRLKQQW**T**D**I**NLKW	Gallus gallus	Chick	MMR, MMRV, TBE, Influenza	61.3
GT--LAVF----------AGRLIELNQQ GT**TN**LAVF**KDGEVIDTACFDIG**GRLI**K**L**D**QQ	Streptococcus pneumoniae		Prevnar 13, Pneumovax23	27.4
PLFSHL--QNEQ PLFSHL**SS**QN**I**Q	Bos taurus	Cow	DTaP/TdaP, MMR,MMRV, IPV, Varivax	26.1
DLVLYNNADGDFAIVK D**F**VLYNNADGDFAIVK	Sus scrofa	Pig	Zostavax	49.8
FLMAHYNRVPALPFPGDPRP FLMAHYN**QA**PALPFPGDPRP	Cavia porcellus	Guinea pig	Varivax	62.6
LWVLRVPSTMVWRPDIVLEN LW**I**LRVPS**A**MVWRPD**V**VLEN	Sus scrofa	Pig	Zostavax	64.3
IVVNAVVVLNVSLRSP IVVNAV**I**VLNVSLR**T**P	Gallus gallus	Chick	MMR, MMRV, TBE, Influenza	46.9
VRKVFLRLLPQLLRMHVR V**H**KVFLRLLPQLLRMHVR	Cavia porcellus	Guinea pig	Varivax	58.3
NRVPALPFPGDPRPYLPSPD NRVPALPFPGDPR**S**YLPS**S**D	Bos taurus	Cow	DTaP/TdaP, MMR,MMRV, IPV, Varivax	60.0
PPAIFRSACSISVTYFPFDW PPAIFRS**S**C**PV**SVTYFPFDW	Sus scrofa	Pig	Zostavax	62.6
FPFDWQNCSLIFQSQTYST FPFDWQNCSL**V**FQSQTYST	Cavia porcellus	Guinea pig	Varivax	66.4
GQTIEWIFIDPEAFTENGEW GQ**D**IEWIFIDPEAFTENGEW	Cavia porcellus	Guinea pig	Varivax	67.7

MG epitopes (14)	Vaccine antigen organism of origin	Common name	Example vaccines containing the antigen	BLASTP Match Score
IHIPSEKIWRPDLVLY IHIPSEKIW**H**PD**F**VLY	Sus scrofa	Pig	Zostavax	49.8
IWRPDVVLYNNADGDFAIVKFTKVLLDYTGHITWT PPAIFKSYCEIIVTHFPFDEQNC IWRPD**L**VLYNNADGDFAIVKFTKVLLDYTGHITWT PPAIFKSYCEIIVTHFPFDEQNC	Bos taurus	Cow	DTaP/TdaP, MMR,MMRV, IPV, Varivax	195
PDTPYLDITYHFVMQRL PDTPYLDITYHF**L**MQRL	Gallus gallus	Chick	MMR, MMRV, TBE, Influenza	58.7
AIFKSYCEIIVTHFPFD AIFKSYCEIIVT**Y**FPFD	Gallus gallus	Chick	MMR, MMRV, TBE, Influenza	56.2
VN---QIVTTNVRLKQQW VN**ERE**QI**M**TTNV**W**LKQEW	Sus scrofa	Pig	Zostavax	37.5
EDHRQVVEVTVGLQLI EDHRQ**A**VEVTVGLQLI	Bos taurus	Cow	DTaP/TdaP, MMR,MMRV, IPV, Varivax	50.3
WNPDDYGGVKKIHIPS WNP**E**DYGGVKKIHIPS	Cavia porcellus	Guinea pig	Varivax	54.5
RGWKHSVTYSCCPDTPY RGWKH**W**V**Y**Y**A**CCPDTPY	Gallus gallus	Chick	MMR, MMRV, TBE, Influenza	49.8
FPFDEQNCSMKLGTWT FPFD**Q**QNCSMKLGTWT	Gallus gallus	Chick	MMR, MMRV, TBE, Influenza	56.2
LKQQWVDYNLKWNPDD LKQQW**T**D**I**NLKWNPDD	Gallus gallus	Chick	MMR, MMRV, TBE, Influenza	49.4
FMESGEWVIKESRGWKH FMESGEWVIKE**A**RGWKH	Sus scrofa	Pig	Zostavax	60.0
QLINVDEVNQI QL**T**NVDEVNQI	Gallus gallus	Chick	MMR, MMRV, TBE, Influenza	35
SEHETRLVAKLFKDY SEHETRLVAKLF**E**DY	Bos taurus	Cow	DTaP/TdaP, MMR,MMRV, IPV, Varivax	46.9
LGTWTYDGSVVAINPES LGTWTYDGSVV**V**INPES	Bos taurus	Cow	DTaP/TdaP, MMR,MMRV, IPV, Varivax	54.1
QYTGHITWTPPAIFKS QY**D**G**M**ITWTPPAIFKS	Sus scrofa	Pig	Zostavax	43.9
FKDYSSVVRPVEDHRQ F**E**DY**N**SVVRPVEDHRQ	Bos taurus	Cow	DTaP/TdaP, MMR,MMRV, IPV, Varivax	48.6
INPESDQPDLSNFMESG INPESD**R**PDLSNFMESG	Gallus gallus	Chick	MMR, MMRV, TBE, Influenza	54.5

MMR (15), MMRV, TBE (16), Zostavax (17), DTaP/TdaP (18–20), Varivax (21), influenza (17).

Discussion

Evidence from bioinformatics and cancer immunology

As seen in Table 1, most chick AchR protein sequences differ from human AchR peptides by just one or two amino acid residues. Thus they are ideally suited to activate human low affinity self reactive (LASR) T cells. These human LASR T cells that recognize human AchR with low affinity can escape the thymus due to positive selection (3). Such T cells with T cell receptors (TCR) that bind with high affinity to chick AchR can be activated by chick AchR proteins, in the presence of innate immune system co-stimulation. Once activated, these T cells interact with B cells and initiate antibody production directed against chick AchR. These antibodies cross react with human AchR to cause MG. The role of LASR T cells in cancer and autoimmunity was previously described (3). Briefly, LASR T cells are involved in humoral and cell mediated immune responses against cancer cells/proteins. That is cells/proteins that are slightly different from self proteins. Cancer involves mutation. Following a mutation, cells produce slightly altered proteins. Since animal proteins look like slightly altered human proteins, the immune system is fooled into activating an anti-cancer response. With an immune response directed against cancer cells/proteins there can always be collateral damage to similar normal cells. With animal protein injection, the immune system begins attacking a non-existent cancer. So only collateral damage occurs.

We verified that all animal epitopes reported in Table 1 did not have 100% homology to any human protein in BLASTP.

Innate immune system co-stimulation during influenza vaccination

Unlike most other inactivated vaccines, most influenza vaccines do not contain an adjuvant. An adjuvant or live virus usually provides the innate immune system co-stimulation required for the vaccine to work.

Influenza vaccines are effective only for a few months (22). Influenza vaccine viral strains can be changed each year. The Advisory Committee on Immunization Practices (ACIP) recommends that when the influenza vaccine is administered for the first time in a person, two doses are required. Since this is only required once in a lifetime, it proves that there is a long term immune response produced by the vaccine. Specifically, the influenza vaccine results in long term persistent IgE mediated sensitization to egg proteins and influenza viral proteins (23–28). The first ever dose provides such sensitization. Subsequent doses elicit an injection site type I immediate IgE mediated hypersensitivity reaction. This reaction provides the innate immune system co-stimulation required for the vaccine to work (sufficient IgG antibody response needed for protection against disease). In other words, the first dose causes the development of egg allergy. The second dose depends on the egg allergy reaction to produce disease protection. This co-stimulation also induces autoimmunity, in the presence of animal proteins such as chick AchR. The subsequent vaccine doses also boost the IgE mediated sensitization (29,30).

Due to the egg protein sensitization based innate immune system co-stimulation mechanism described above, the egg-free Flublok (31) vaccine would fail to work. Since Flublok contains no egg proteins, the innate immune system is not stimulated. The Flublok vaccine would only provide feeble protection. That is why the Flublok vaccine was approved with 3X the hemagglutinin (HA) antigen quantity as the regular chick egg derived vaccines. The Flublok vaccine contains 45 μg of HA protein per virus strain vs. only 15 μg of HA protein in a regular influenza vaccine.

So far no cases of MG have been reported against egg-free Flublok (insect derived) and Flucelvax (Madin Darby canine kidney cell derived) influenza vaccines (32) in the VAERS. MG cannot be ruled with these vaccines because (i) they have been only used for a short period of time with fewer doses administered and (ii) they are contaminated with other animal and insect proteins which can include AchR.

Evidence from VAERS

Influenza vaccines

VAERS was searched using the following "symptom" terms: Myasthenia Gravis, Ocular Myasthenia, Myasthenia Syndrome and Myasthenia Gravis crisis. We will refer to these as myasthenic disorders (MD). The disease onset interval obtained from VAERS shows clustering of MD reports starting day 0 and rapidly declining with time (Figure 1). Thus making it absolutely clear that they are vaccine induced.

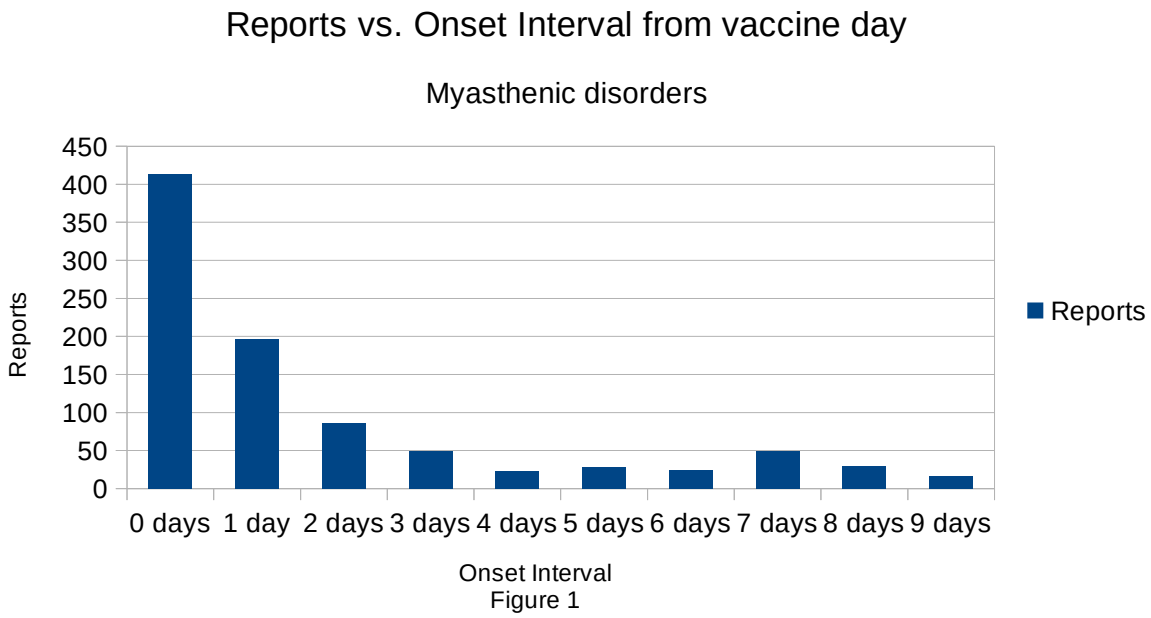


Figure 1

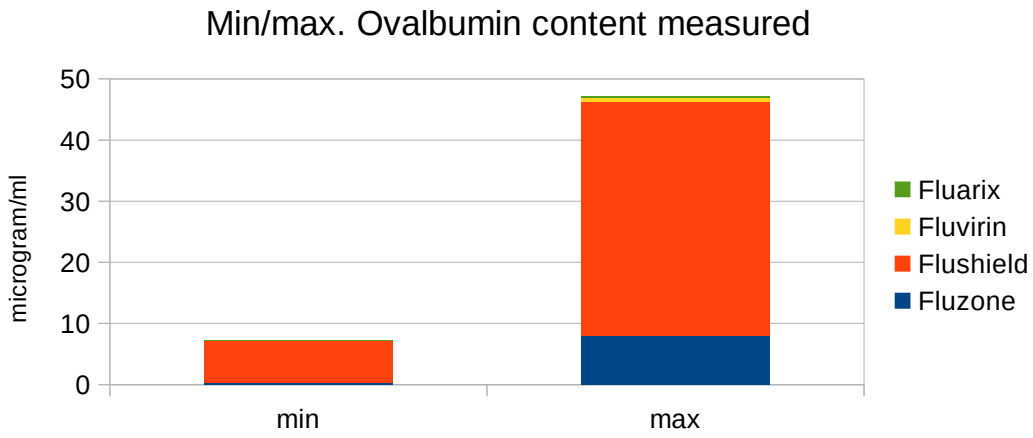


Figure 2

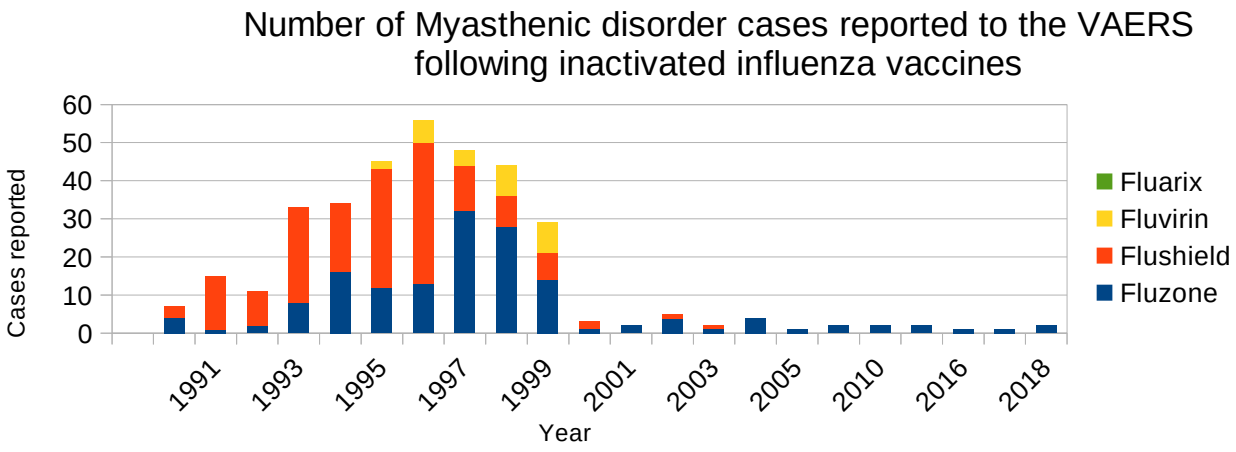


Figure 3

VAERS data shows 497 reports of MG or myasthenic syndrome following influenza vaccine administration. Goldis et al (6). reported the level of egg protein contamination in influenza vaccines in 2010. They reported that the Flushield vaccine contained, 6.90-38.30 µg/ml; Fluarix, 0.025-0.31 µg/ml; Fluzone®, 0.30-8.05 µg/ml; Fluvirin®, <0.01-0.55 µg/ml, all in 1997/98. This is plotted in Figure 2. Goldis et al. report "undetectable" levels of ovalbumin in influenza vaccines measured in 2010. Figure 3 shows Myasthenia disorder cases reported against each vaccine brand. Ovalbumin content of the vaccine shows correlation to reported cases. Ovalbumin is a major egg protein but there are thousands of proteins in chicken egg. Ovalbumin is a surrogate marker representing all egg proteins (24). So we are seeing correlation between the amount of chick acetylcholine receptor protein and MuSK protein in the vaccine to the number of MD cases reported. Tackenberg et al. (5) measured AchR antibody levels before and after influenza vaccine administration in 31 subjects most of whom were on immunosuppressive therapy. Even in this population, two subjects developed increased levels of AchR by ~20% and ~80% respectively. Clearly demonstrating that immunizing with chick AchR proteins boost AchR antibody levels. Such antibody level boosting has been reported for other contaminating proteins in vaccines such as food proteins (29,30,33) and bovine serum albumin (BSA) in equine vaccines (34).

Referring to Figure 3, why did the cases drop suddenly in 2000? The most likely explanation is that European regulators were in talks with vaccine vendors to introduce an ovalbumin limit of 2 µg/ml (1 µg per dose) in influenza vaccines, which was introduced in 2002 (35). This action was related to increased allergic reactions in egg allergic vaccine recipients. So vaccine makers seem to have started cleaning up egg contamination to meet the upcoming regulation.

Other vaccines

Similar to the influenza vaccine, other vaccines are also contaminated with numerous animal proteins and contain AchR proteins thus resulting in MD. As shown in Table 1, these vaccines include many bovine, porcine, chick or guinea pig protein containing vaccines. Further, HBV/HPV vaccines contain yeast proteins that have molecular mimicry to human MuSK protein. As shown in Table 1, some pneumococcal proteins also have homology to human AchR.

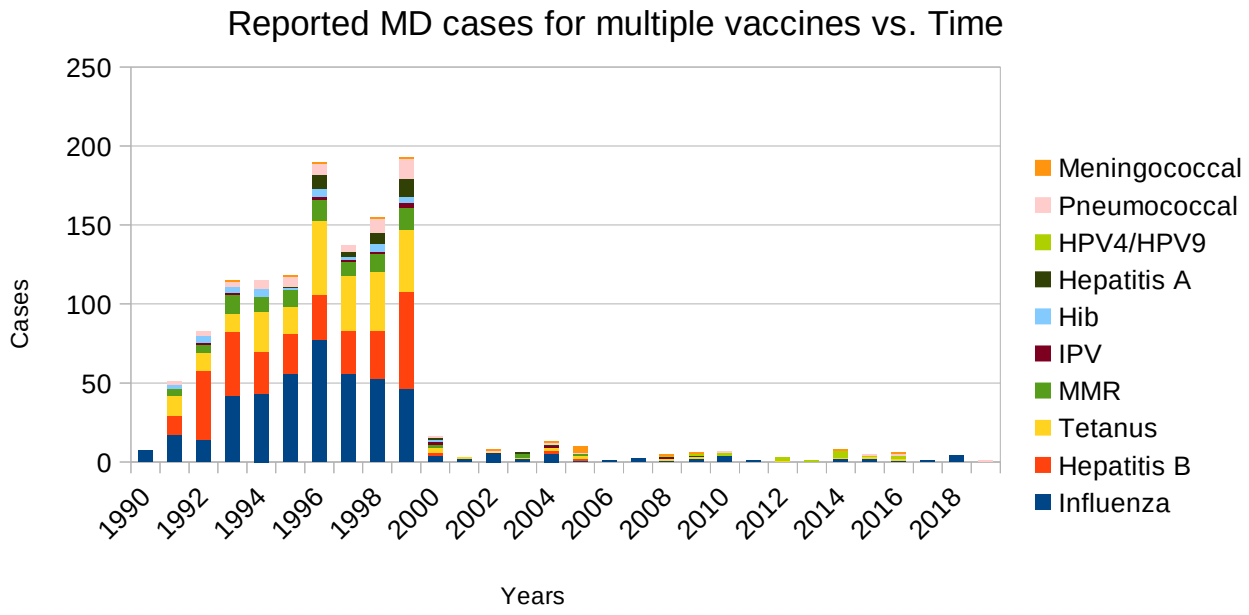


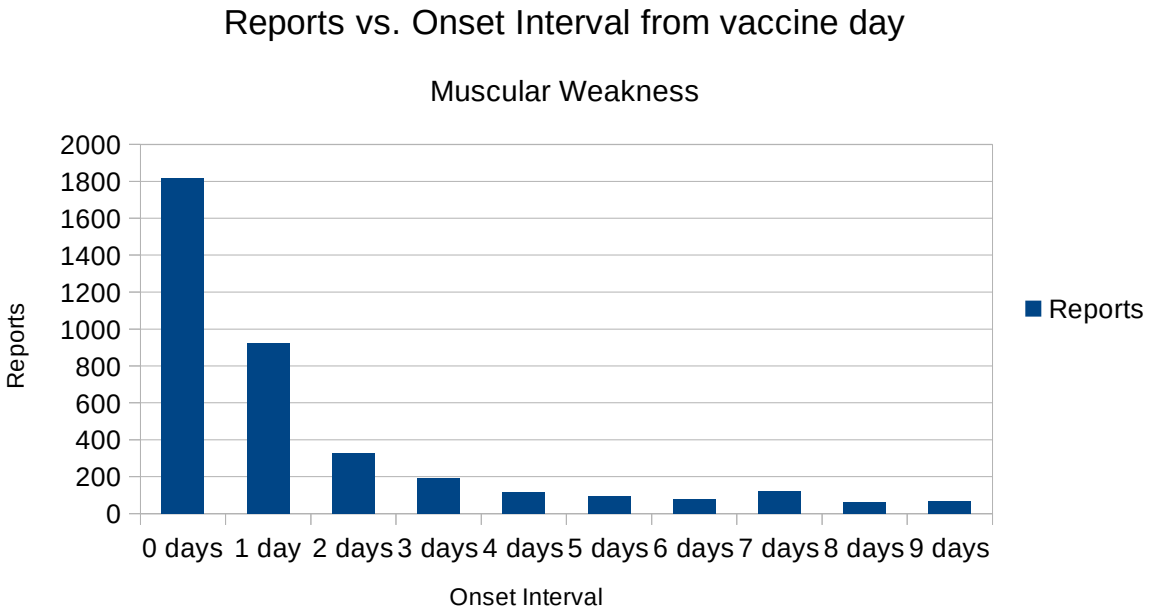
Figure 4

Figure 4 shows VAERS data of MD cases reported against various vaccines. Cases for all vaccines show a sharp decline in the year 2000. It is unlikely that the content of all vaccines were altered in 2000. The likely explanation is that the influenza vaccine being the most administered was responsible for sensitization to AchR and MuSK proteins. All other vaccines are relatively minor contributors to sensitization. However, once sensitized, given the cross reactivity among animal and human peptides, all vaccines boosted antibody level upon administration thus resulting in the adverse events. Once sensitization was reduced by reducing egg protein in the influenza vaccines, antibody boosting related adverse events also dropped. Other than antigens in Table 1, here are more instances of molecular mimicry that may also play a role:

Vaccine	Vaccine antigen organism of origin	Human self protein	BLASTP Match Score
Meningococcal	*N. meningitidis*	AchR	26.2
Hepatitis B, HPV vaccine	*S. cerevisiae*	MuSK	84.3
MMR, MMRV, TBE	*Gallus gallus*	MuSK	1189.0

Muscular Weakness and Myasthenic Disorders

Searching for muscular weakness reports in VAERS produced some interesting data. Muscular weakness may simply be milder cases of myasthenia syndrome reported to the VAERS. Reducing egg protein content in influenza vaccines seems to have replaced myasthenic disorder domination with muscular weakness domination, around the year 2000. Those diagnosed with muscular weakness likely have low levels of AchR or MuSK antibodies and will suffer neuromuscular joint damage with time and disease progression. Eventual myasthenic disorder diagnosis may not be reported to VAERS.



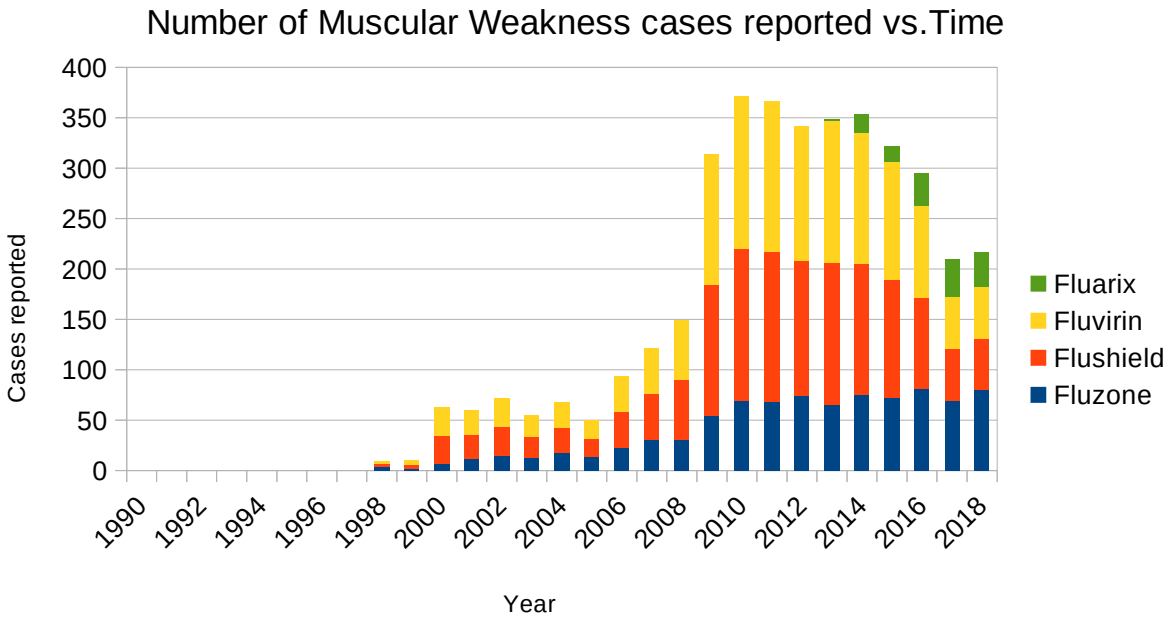


Figure 7

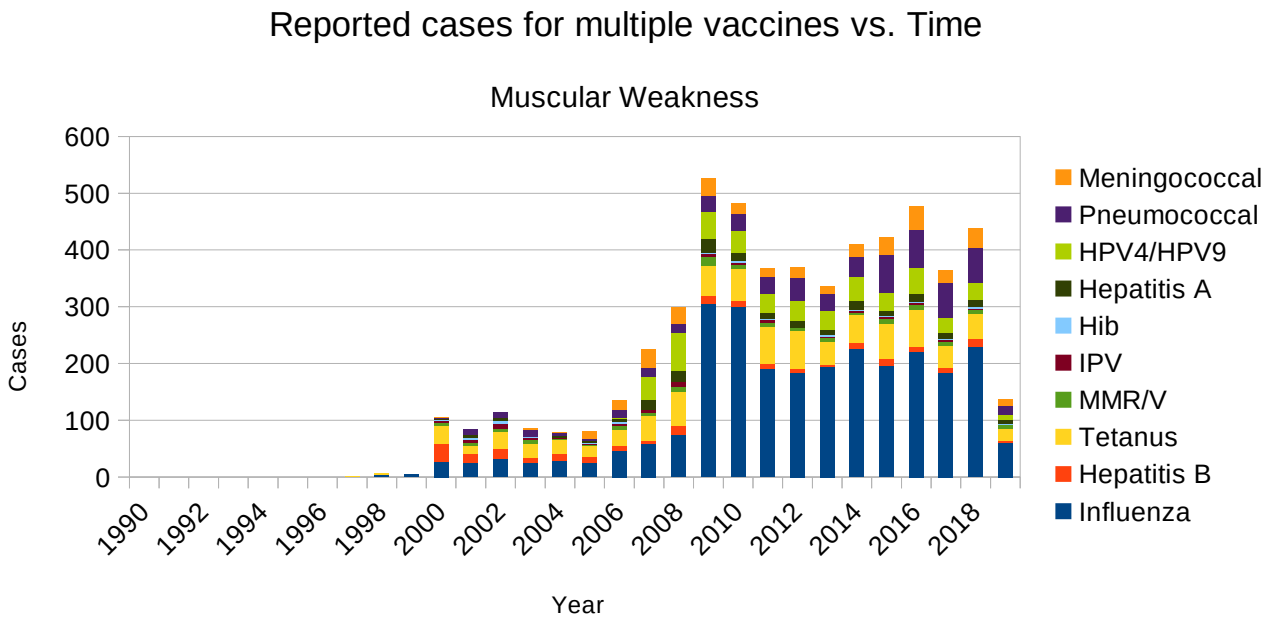


Figure 6

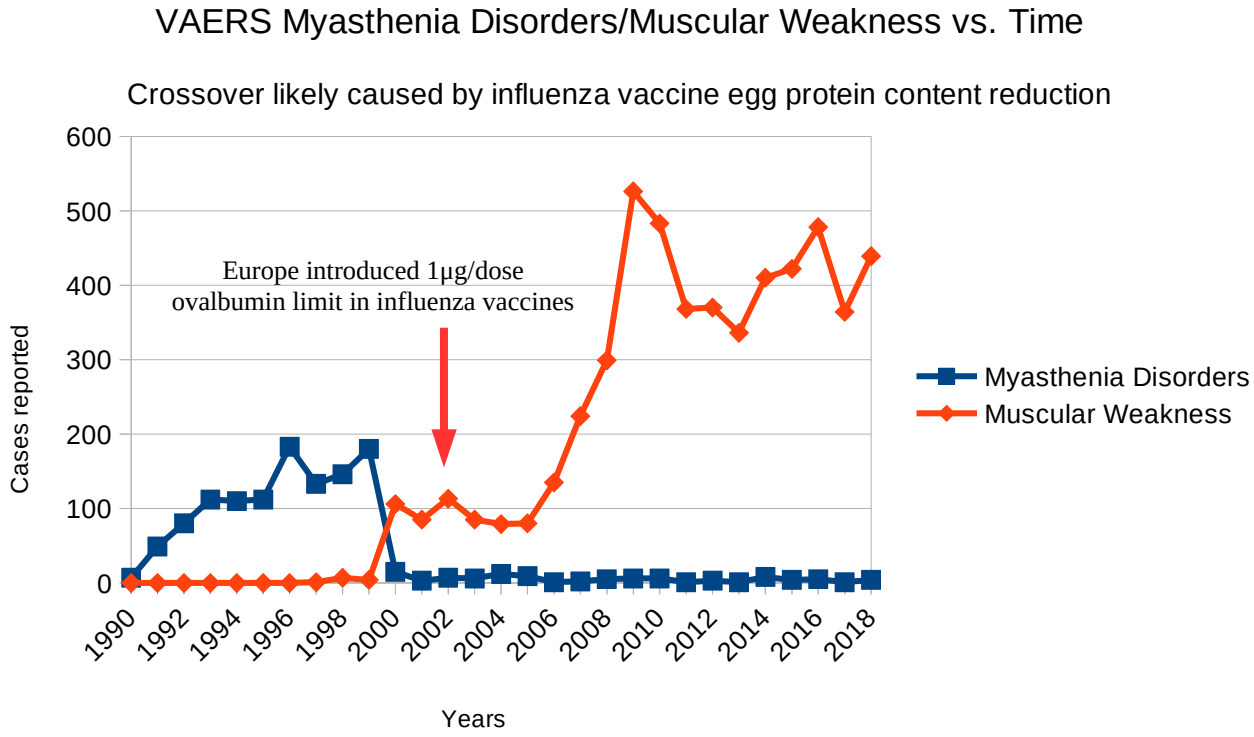


Figure 8

Evidence from titer study

Tackenberg et al (5). report 20-81.2% AchR antibody titer increase in 2 out of 31 patients following chicken egg derived influenza vaccine administration. Most of the patients were on immunosuppressive treatment. The influenza vaccine used was Mutagrip from Sanofi Pasteur, obtained over the three year study period ending 2018. If Goldis et al. observation of “undetectable” egg protein contamination in 2010 were still applicable in 2018, these vaccines are still inducing AchR antibodies.

If healthy patients with no immunosuppressive treatment were studied, we can expect more vaccine recipients to develop antibodies, even higher levels of AchR titers and thus increased risk of MG.

Evidence from case reports

We have multiple case reports of MG development following HBV and HPV vaccines (36–40).

Thymic involvement

There is a debate on the role of the thymus in MG. Thymectomy helps in some cases of MG. Some have argued that MG disease (autosensitization) originates in the thymus and not the periphery (41,42). The evidence presented above contradicts that notion. Vaccine induced MG originates in the periphery. In other words, autosensitization occurs in peripheral lymph nodes. The myoid cells in the thymus express AchR receptors and therefore will be affected by vaccine induced anti-AchR antibodies. Such an autoimmune, autoinflammatory process in the thymus can lead to thymic changes observed in MG that play a role in sustaining the disease. This can explain the beneficial effect of thymectomy in some cases.

Graves’ Disease

Inaba et al. (43) identified autoepitopes involved in Graves’ disease. As before, BLASTP analysis was run comparing these autoepitopes to vaccine antigens. Similar to the results for MG, we see many peptides differ from homologous human epitopes by 1,2 or 3 amino acid residues. So the same mechanism of disease causation as in MG, applies here.

Graves’ epitopes (43)	Vaccine antigen organism of origin	Common name	Example vaccines containing the antigen	BLASTP Match Score
IDVTLQQLE IDVTL**K**Q**I**E	Saccharomyces cerevisiae	Yeast	HBV, HPV	24.0
ISRIYVSIDVTLQQLES ISRIY**L**SID**A**TLQQLES	Sus scrofa	Pig	Zostavax	49.4
ISRIYVSIDVTLQQLES ISRIY**L**SID**A**TLQQLES	Chlorocebus aethiops	African Green Monkey	Polio	49.4
ISRIYVSIDVTLQQLES ISRIY**L**SID**A**TLQQLES	Bos taurus	Cow	DTaP/TdaP, MMR,MMRV, IPV, Varivax	49.4
ISRIYVSIDVTLQQLES ISRIY**L**SID**T**TLQ**R**LES	Cavia porcellus	Guinea Pig	Varivax	44.8

Graves' epitopes (43)	Vaccine antigen organism of origin	Common name	Example vaccines containing the antigen	BLASTP Match Score
ISRIYVSIDVTLQQLE ISRIY**I**SID**E**TLQ**S**LE	Gallus gallus	Chick	MMR, MMRV, TBE, Influenza	41.4
GIFNTGLKMFPDLTKVYST GIFNTGL**RI**FPDLTKVYST	Sus scrofa	Pig	Zostavax	56.6
GIFNTGLKMFPDLTKVYST GIFNTGL**TI**FPDLTKVYST	Cavia porcellus	Guinea Pig	Varivax	55.4
GIFNTGLKMFPDLTKVYST GIFNTGL**RV**FPDLTK**I**YST	Bos taurus	Cow	DTaP/TdaP, MMR,MMRV, IPV, Varivax	54.5
GIFNTGLKMFPDLTKVYS GIFNTGLK**V**FPDLTK**I**YS	Gallus gallus	Chick	MMR, MMRV, TBE, Influenza	54.5
GIFNTGLKMFPDLTKV GIF**D**T**A**L**R**MF**GEMQ**KV	Glycine max	Soy	Prevnar 13	29.9
NTGL---KMFPDLTK **D**TGL**PTA**KMF**T**DLTK	Streptococcus pneumoniae		Prevnar 13, Pneumovax23	29.5
IFNTGLKM IF**K**TGLKM	Haemophilus influenzae		ActHib	26.1
LK--MFPDLTK LK**KG**MFP**N**LTK	Arachis hypogaea	Peanut	Any (44)	26.1
FNTGLKMFPDLTKVY F**H**T-LKMF**RS**L**NN**VY	Saccharomyces cerevisiae	Yeast	HBV, HPV	25.7

Iatrogenic cascade

Nakajima et al. (45) report the case of a patient with T1D that developed MG after 5 years and developed GD 15 years later.

As shown above, immunization with yeast (*S. cerevisiae*) can be expected to cause MG and GD. Since insulin is manufactured using yeast (*S. cerevisiae*), insulin for injections contain residual yeast proteins. T1D patients who routinely have to inject insulin, develop anti-saccharomyces cerevisiae antibodies (ASCA) (10). So it comes as no surprise that T1D patients go on to develop MG and GD.

Conclusion

The VAERS being a passive surveillance system is known to be affected by underreporting. Even with such underreporting, there are ~1500 MD cases reported and ~6000 cases of muscle weakness which may be related to MD. It is likely that there are hundreds of thousands of vaccine-induced cases that go unreported because symptom onset was delayed. An even larger number of people can be expected to have sub-clinical damage. The damage caused by such contaminated vaccines is therefore enormous. Current evaluations of vaccine safety profiles ignore these major adverse events, paint a rosy picture and continue to claim that the benefits outweigh the risk. A claim that is not supported by the evidence.

The findings described add to the evidence that non-target antigens (NTA) in vaccines cause numerous disorders. NTA are usually ignored in vaccine safety studies. Reducing such antigens show reduction in the rates of diseases they cause. Japan removed gelatin from vaccines as the ultimate solution to vaccine induced gelatin allergy (46,47). H1N1 nucleoprotein, another NTA in the Pandemrix vaccine sickened thousands with narcolepsy (48–51). Arepanrix vaccine manufactured by the same vendor in a different facility, contained less H1N1 nucleoprotein and resulted in fewer such adverse events. Vaccine regulators refuse to learn from such failures and continue to sicken millions with NTA contaminated vaccines (52–54). Vaccine safety claims are solely based on fundamentally flawed epidemiological studies (55). The Institute of Medicine has concluded that these epidemiological studies fail to provide sufficient evidence in an overwhelming 93% of the cases (56). In contrast, numerous vaccines are being implicated in autoimmune disorders when reviewing case reports (57). The findings here prove that the highly touted post-marketing vaccine safety surveillance and pharmacovigilance systems are an abject failure.

All NTA should be immediately removed from all vaccines using technologies such as affinity chromatography (58).

References

1. Patrick J, Lindstrom J. Autoimmune response to acetylcholine receptor. Science. American Association for the Advancement of Science; 1973 May 25;180(4088):871–2.
2. Milani M, Ostlie N, Wu H, Wang W, Conti-Fine BM. CD4+ T and B cells cooperate in the immunoregulation of Experimental Autoimmune Myasthenia Gravis. J Neuroimmunol. 2006 Oct;179(1-2):152–62.
3. Arumugham V, Trushin M V. Cancer immunology, bioinformatics and chemokine evidence link vaccines contaminated with animal proteins to autoimmune disease: a detailed look at Crohn’s disease and Vitiligo. J Pharm Sci Res. 2018;10(8):2106.
4. American Academy of Neurology. N, Hanumanthu R, Shah S, Souayah N. Neurology. Neurology. Advanstar Communications; 2018. P6.437 p.
5. Tackenberg B, Schneider M, Blaes F, Eienbröker C, Schade-Brittinger C, Wellek A, et al. Acetylcholine Receptor Antibody Titers and Clinical Course after Influenza Vaccination in Patients with Myasthenia Gravis: A Double-Blind Randomized Controlled Trial (ProPATIent-Trial). EBioMedicine. 2018 Feb;28:143–50.
6. Goldis M, Bardina L, Lin J, Sampson HA. Evaluation of Egg Protein Contamination in Influenza Vaccines. J Allergy Clin Immunol. 2010;
7. Smith MA, Slater CR. Spatial distribution of acetylcholine receptors at developing chick neuromuscular junctions. J Neurocytol. Kluwer Academic Publishers; 1983 Dec;12(6):993–1005.
8. Paterson B, Prives J. APPEARANCE OF ACETYLCHOLINE RECEPTOR IN DIFFERENTIATING CULTURES OF EMBRYONIC CHICK BREAST MUSCLE. J Cell Biol. 1973 Oct 1;59(1):241–5.
9. Giacobini Robecchi MG, Sisto Daneo L, Filogamo G. [Acetylcholine receptors in chick embryo somites]. Bull Assoc Anat (Nancy). 1984 Mar;68(200):41–4.

10. Sakly W, Mankaï A, Sakly N, Thabet Y, Achour A, Ghedira-Besbes L, et al. Anti-Saccharomyces cerevisiae Antibodies are Frequent in Type 1 Diabetes. Endocr Pathol. 2010 Jun 13;21(2):108–14.

11. UniProt: the universal protein knowledgebase. Nucleic Acids Res. 2017 Jan 4;45(D1):D158–69.

12. Altschul SF, Madden TL, Schäffer AA, Zhang J, Zhang Z, Miller W, et al. Gapped BLAST and PSI-BLAST: a new generation of protein database search programs. Nucleic Acids Res. 1997;25(17):3389–402.

13. The Vaccine Adverse Event Reporting System (VAERS) Request Form [Internet]. [cited 2019 Sep 4]. Available from: https://wonder.cdc.gov/controller/datarequest/D8;jsessionid=447B43486F1720811AF4BB727EE4F8DC

14. Vaughan K, Kim Y, Sette A. A comparison of epitope repertoires associated with myasthenia gravis in humans and nonhuman hosts. Autoimmune Dis. Hindawi; 2012 Dec 2;2012:403915.

15. Fda, Cber. M-M-R ® II (MEASLES, MUMPS, and RUBELLA VIRUS VACCINE LIVE) [Internet]. [cited 2019 Aug 30]. Available from: https://www.fda.gov/media/75191/download

16. Package leaflet: Information for the user TicoVac 0.5 ml Suspension for injection in a pre-filled syringe Tick-Borne Encephalitis Vaccine (whole virus inactivated) [Internet]. [cited 2019 Aug 30]. Available from: https://www.medicines.org.uk/emc/files/pil.1923.pdf

17. CDC. Vaccine Excipient Summary [Internet]. [cited 2019 Sep 11]. Available from: https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/b/excipient-table-2.pdf

18. Pasteur S. Adacel Package Insert [Internet]. 2005. Available from: https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm142764.pdf

19. Glaxo Smith Kline. Infanrix package insert [Internet]. Available from: https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm124514.pdf

20. Glaxo Smith Kline. Boostrix Package Insert [Internet]. 2005. Available from: https://www.fda.gov/downloads/BiologicsBloodVaccines/UCM152842.pdf

21. Fda, Cber. Package Insert - Varivax (Refrigerator) [Internet]. Available from:

https://www.fda.gov/media/76008/download

22. Ferdinands JM, Fry AM, Reynolds S, Petrie J, Flannery B, Jackson ML, et al. Intraseason waning of influenza vaccine protection: Evidence from the US Influenza Vaccine Effectiveness Network, 2011-12 through 2014-15. Clin Infect Dis. 2017 Dec 1;64(5):544–50.

23. Yamane N, Uemura H. Serological examination of IgE- and IgG-specific antibodies to egg protein during influenza virus immunization. Epidemiol Infect. Cambridge University Press; 1988 Apr;100(2):291–9.

24. Kürsteiner O, Moser C, Lazar H, Durrer P. Inflexal® V—The influenza vaccine with the lowest ovalbumin content. Vaccine. 2006 Nov;24(44-46):6632–5.

25. Nagao M, Fujisawa T, Ihara T, Kino Y. Highly increased levels of IgE antibodies to vaccine components in children with influenza vaccine-associated anaphylaxis. J Allergy Clin Immunol. United States; 2016 Mar;137(3):861–7.

26. Nakayama T, Kumagai T, Nishimura N, Ozaki T, Okafuji T, Suzuki E, et al. Seasonal split influenza vaccine induced IgE sensitization against influenza vaccine. Vaccine. 2015 Nov 9;33(45):6099–105.

27. Davidsson A, Eriksson JC, Rudblad S, Brokstad KA. Influenza Specific Serum IgE is Present in Non-Allergic Subjects. Scand J Immunol. 2005 Dec;62(6):560–1.

28. Smith-Norowitz TA, Wong D, Kusonruksa M, Norowitz KB, Joks R, Durkin HG, et al. Long term persistence of IgE anti-influenza virus antibodies in pediatric and adult serum post vaccination with influenza virus vaccine. Int J Med Sci. Ivyspring International Publisher; 2011 Mar 18;8(3):239–44.

29. Hoyt AEW. Presentation: Changes in IgE Levels Following One-Year Immunizations in Two Children with Food Allergy (WAO Symposium on Food Allergy & the Microbiome). 2018.

30. Arumugham V. Vaccines and the development of food allergies: the latest evidence [Internet]. BMJ. 2016. Available from: https://www.bmj.com/content/355/bmj.i5225/rr-0

31. Corporation PS. Flublok Quadrivalent 2017-2018 [Internet]. 2018. Available from: https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM619551.pdf

32. Flucelvax Quadrivalent | FDA [Internet]. [cited 2019 Sep 9]. Available from: https://www.fda.gov/vaccines-blood-biologics/vaccines/flucelvax-quadrivalent

33. Hoyt AEW, Schuyler AJ, Heymann PW, Platts-Mills TAE, Commins SP. Alum-Containing Vaccines Increase Total and Food Allergen-Specific IgE, and Cow’s Milk Oral Desensitization Increases Bosd4 IgG4 While Peanut Avoidance Increases Arah2 IgE: The Complexity of Today's Child with Food Allergy. J Allergy Clin Immunol. Elsevier; 2017 Jul 7;137(2):AB151.

34. Gershwin LJ, Netherwood KA, Norris MS, Behrens NE, Shao MX. Equine IgE responses to non-viral vaccine components. Vaccine. Netherlands; 2012 Dec;30(52):7615–20.

35. Kong H, Wong S, Yuen KY. Influenza vaccination: options and issues. Hong Kong Med J. *+; 2005.

36. Chung JY, Lee SJ, Shin B-S, Kang HG. Myasthenia gravis following human papillomavirus vaccination: a case report. BMC Neurol. BioMed Central; 2018 Dec 28;18(1):222.

37. Stübgen J-P. Neuromuscular disorders associated with Hepatitis B vaccination. J Neurol Sci. Elsevier; 2010 May 15;292(1):1–4.

38. Louzir B, Othmani S, Battikh R, Abdelhafidh N Ben, Bahri M, Taalouche L, et al. Myasthénie après vaccination antihépatite B. Therapies. Elsevier; 2003 Jul 1;58(4):378–9.

39. Biron P, Montpetit P, Infante-Rivard C, Léry L. Myasthenia gravis after general anesthesia and hepatitis B vaccine. Arch Intern Med. 1988 Dec;148(12):2685.

40. Bahri M, Louzir B, Othmani S, Battikh R, Bahri M. FRI0248 Myasthenia gravis after hepatitis b vaccine. report of one case. Ann Rheum Dis. BMJ Publishing Group Ltd; 2001 Jun 1;60(Suppl 1):A226–7.

41. Cavalcante P, Le Panse R, Berrih-aknin S, Maggi L, Antozzi C, Baggi F, et al. The thymus in myasthenia gravis: Site of “innate autoimmunity”? Muscle Nerve. John Wiley & Sons, Ltd; 2011 Oct 1;44(4):467–84.

42. Cordiglieri C, Marolda R, Franzi S, Cappelletti C, Giardina C, Motta T, et al. Innate immunity in myasthenia gravis thymus: Pathogenic effects of Toll-like receptor 4 signaling on autoimmunity. J Autoimmun. 2014 Aug;52:74–89.

43. Inaba H, Groot LJ De, Akamizu T. Thyrotropin Receptor Epitope and Human Leukocyte Antigen in Graves' Disease. Front Endocrinol (Lausanne). Frontiers Media SA; 2016;7.

44. National Academies of Sciences and Medicine E. Finding a Path to Safety in Food Allergy: Assessment of the Global Burden, Causes, Prevention, Management, and Public Policy. Stallings VA, Oria MP, editors. Washington, DC: The National Academies Press; 2017.

45. Nakajima S, Matsunaga M, Shibata M, Kusada N, Nakashima K, Inagaki A, et al. A Case of Autoimmune Type 1 Diabetes Mellitus Complicated by Myasthenia Gravis and Graves' Disease. J Japan Diabetes Soc. 2015;58(3):198–204.

46. Kuno-Sakai H, Kimura M. Removal of gelatin from live vaccines and DTaP-an ultimate solution for vaccine-related gelatin allergy. Biologicals. 2003 Dec;31(4):245–9.

47. Nakayama T, Aizawa C, Kuno-Sakai H. A clinical analysis of gelatin allergy and determination of its causal relationship to the previous administration of gelatin-containing acellular pertussis vaccine combined with diphtheria and tetanus toxoids. J Allergy Clin Immunol. Elsevier; 1999 Jan 9;103(2):321–5.

48. Ahmed SS, Volkmuth W, Duca J, Corti L, Pallaoro M, Pezzicoli A, et al. Antibodies to influenza nucleoprotein cross-react with human hypocretin receptor 2. Sci Transl Med. 2015 Jul 1;7(294):294ra105–294ra105.

49. Arumugham V. Pandemrix and Arepanrix vaccine safety analysis and scrutiny fell short [Internet]. The BMJ. 2018. Available from: https://www.bmj.com/content/363/bmj.k4152/rr-14

50. Arumugham V. Pharmacovigilance is no substitute for good vaccine design [Internet]. The BMJ. 2018. Available from: https://www.bmj.com/content/362/bmj.k3948/rr-11

51. Arumugham V. SIDS, Kawasaki Disease and narcolepsy: Same mechanism, different vaccines [Internet]. The BMJ. 2018. Available from: https://www.bmj.com/content/360/bmj.k1378/rr-11

52. Arumugham V. Vaccines and Biologics injury table based on mechanistic evidence – Mar 2019 [Internet]. 2019 [cited 2019 May 16]. Available from:

https://zenodo.org/record/2582635/files/viittoc0302http.pdf?download=1

53. Arumugham V. Role of animal, food, fungal protein containing vaccines, insulin injections and gastric acid inhibition therapy in the etiology of celiac disease [Internet]. 2019 [cited 2019 Aug 24]. Available from: https://doi.org/10.5281/zenodo.3370427

54. Arumugham V. Autoepitopes (22 of 27) in rheumatoid arthritis differ from vaccine antigens by a single amino acid residue, ideal for low affinity self reactive T cell mediated autoimmunity and aluminum adjuvant promotes citrullination of vaccine antigens thus the synthesis of ACPA [Internet]. 2019 [cited 2019 Sep 10]. Available from: https://doi.org/10.5281/zenodo.3382978

55. Arumugham V. Vaccine safety: Learning from the Boeing 737 MAX disasters [Internet]. 2019 [cited 2019 May 2]. Available from: https://doi.org/10.5281/zenodo.2648251

56. Arumugham V. Institute of Medicine: Most epidemiological vaccine safety studies are useless [Internet]. 2019 [cited 2019 Jun 12]. Available from: https://doi.org/10.5281/zenodo.3244496

57. Vanood A, Wingerchuk D. Systematic Review Investigating Relationship Between Neuromyelitis Optica Spectrum Disorder (NMOSD) and Vaccination (P1.2-003). Neurology. Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology; 2019;92(15 Supplement).

58. Zhao M, Vandersluis M, Stout J, Haupts U, Sanders M, Jacquemart R. Affinity chromatography for vaccines manufacturing: Finally ready for prime time? Vaccine. Netherlands; 2018 Apr;