

Referencias bibliográficas, english abstract y breve resumen en castellano de los artículos referenciados

1. [Miller NZ, Goldman GS. 2011. Infant mortality rates regressed against number of vaccine doses routinely given: Is there a biochemical or synergistic toxicity? Human and Experimental Toxicology. 30(9): 1420-1428]

Abstract

The infant mortality rate (IMR) is one of the most important indicators of the socio-economic well-being and public health conditions of a country. The US childhood immunization schedule specifies 26 vaccine doses for infants aged less than 1 year—the most in the world—yet 33 nations have lower IMRs. Using linear regression, the immunization schedules of these 34 nations were examined and a correlation coefficient of $r = 0.70$ ($p < 0.0001$) was found between IMRs and the number of vaccine doses routinely given to infants. Nations were also grouped into five different vaccine dose ranges: 12–14, 15–17, 18–20, 21–23, and 24–26. The mean IMRs of all nations within each group were then calculated. Linear regression analysis of unweighted mean IMRs showed a high statistically significant correlation between increasing number of vaccine doses and increasing infant mortality rates, with $r = 0.992$ ($p = 0.0009$). Using the Tukey-Kramer test, statistically significant differences in mean IMRs were found between nations giving 12–14 vaccine doses and those giving 21–23, and 24–26 doses. A closer inspection of correlations between vaccine doses, biochemical or synergistic toxicity, and IMRs is essential.

-La tasa de mortalidad infantil (TMI) es un indicador del bienestar socioeconómico y de la salud pública de un país. En EEUU, se especifican 26 dosis en el calendario de vacunación infantil para lactantes menores de 1 año, y aún y así, hay 33 naciones con menor TMI.

-Se examinaron los calendarios de vacunación de 34 naciones y se hizo un estudio de regresión lineal. Se encontró un coeficiente de correlación de $r = 0,70$ entre TMI y el número de dosis de vacunas de rutina dada a los infantes.

-También agrupamos las naciones en cinco rangos diferentes de dosis de vacuna: 12-14, 15-17, 18-20, 21-23, 24-26. Los medios de TMI se calcularon para todas las naciones dentro de cada grupo.

-El análisis de regresión lineal reveló una alta correlación estadísticamente significativa entre el aumento del número de dosis de vacunas y el aumento de las TMI.

-La siguiente figura del artículo muestra la regresión lineal entre el número de dosis de vacunas con la TMI:

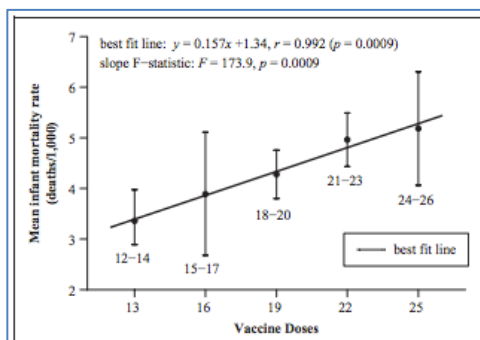


Figure 2. 2009 Mean infant mortality rates and mean number of vaccine doses (five categories).

2. [Goldman GS, Miller NZ. 2012. Relative trends in hospitalizations and mortality among infants by the number of vaccine doses and age, based on the Vaccine Adverse Event Reporting System (VAERS), 1990-2010. Human and Experimental Toxicology. 31(10): 1012-1021]

Abstract

In this study, the Vaccine Adverse Event Reporting System (VAERS) database, 1990–2010, was investigated; cases that specified either hospitalization or death were identified among 38,801 reports of infants. Based on the types of vaccines reported, the actual number of vaccine doses administered, from 1 to 8, was summed for each case. Linear regression analysis of hospitalization rates as a function of (a) the number of reported vaccine doses and (b) patient age yielded a linear relationship with $r^2 = 0.91$ and $r^2 = 0.95$, respectively. The hospitalization rate increased linearly from 11.0% (107 of 969) for 2 doses to 23.5% (661 of 2817) for 8 doses and decreased linearly from 20.1% (154 of 765) for children aged <0.1 year to 10.7% (86 of 801) for children aged 0.9 year. The rate ratio (RR) of the mortality rate for 5–8 vaccine doses to 1–4 vaccine doses is 1.5 (95% confidence interval (CI), 1.4–1.7), indicating a statistically significant increase from 3.6% (95% CI, 3.2–3.9%) deaths associated with 1–4 vaccine doses to 5.5% (95% CI, 5.2–5.7%) associated with 5–8 vaccine doses. The male-to-female mortality RR was 1.4 (95% CI, 1.3–1.5). Our findings show a positive correlation between the number of vaccine doses administered and the percentage of hospitalizations and deaths. Since vaccines are given to millions of infants annually, it is imperative that health authorities have scientific data from synergistic toxicity studies on all combinations of vaccines that infants might receive. Finding ways to increase vaccine safety should be the highest priority.

- En este estudio, se investigó la base de datos del VAERS (Sistema de reporte de efectos adversos de vacunas) desde 1990 – 2010.
- 38.801 casos fueron identificados de hospitalizaciones o muerte en lactantes causadas por vacunaciones.
- Se hizo un análisis de regresión lineal de las tasas de hospitalización como una función de a) el número de dosis de vacuna y b) la edad del paciente.
- Nuestros resultados muestran una correlación positiva entre el número de dosis de vacunas administradas y el porcentaje de hospitalizaciones y muertes.
- Considerando el número de vacunas administradas a millones de bebés al año, es imperativo que las autoridades sanitarias dispongan de los datos de estudios toxicológicos sobre todas las combinaciones de vacunas que puedan recibir los niños. Encontrar maneras de aumentar la seguridad de las vacunas debe ser la máxima prioridad.

3. [Classen JB, Classen DC. 2002. Clustering of Cases of Insulin Dependent Diabetes (IDDM) Occurring Three Years After Hemophilus Influenza B (HiB) Immunization Support Causal Relationship Between Immunization and IDDM. Autoimmunity. 35(4): 247-253]

Objective: The hemophilus vaccine has been linked to the development of autoimmune type 1 diabetes, insulin dependent diabetes (IDDM) in ecological studies.

Methods: We attempted to determine if the Hemophilus influenza B (HiB) vaccine was associated with an increased risk of IDDM by looking for clusters of cases of IDDM using data from a large clinical trial. All children born in Finland between October 1st, 1985 and August 31st, 1987, approximately 116,000 were randomized to receive 4 doses of the HiB vaccine (PPR-D, Connaught) starting at 3 months of life or one dose starting after 24 months of life. A control-cohort included all 128,500 children born in Finland in the 24 months prior to the HiB vaccine study. Non-obese diabetic prone (NOD) mice were immunized with a hemophilus vaccine to determine if immunization increased the risk of IDDM.

Results: The difference in cumulative incidence between those receiving 4 doses and those receiving 0 doses is 54 cases of IDDM/100,000 ($P = 0.026$) at 7 years, (relative risk = 1.26). Most of the extra cases of IDDM appeared in statistically significant clusters that occurred in periods starting approximately 38 months after immunization and lasting approximately 6–8 months. Immunization with pediatric vaccines increased the risk of insulin diabetes in NOD mice.

Conclusion: Exposure to HiB immunization is associated with an increased risk of IDDM. NOD mice can be used as an animal model of vaccine induced diabetes.

- La vacuna Haemophilus se ha relacionado con el desarrollo de diabetes autoinmune tipo 1 (DMID) en estudios ecológicos.
- Tratamos de determinar si el Haemophilus influenza B (HiB) se asoció con un mayor riesgo de DMID mediante la búsqueda de grupos de casos de DMID utilizando datos de un ensayo clínico a gran escala. Todos los niños nacidos en Finlandia entre el 01 de octubre 1985 y el 31 de agosto de 1987, aproximadamente 116.000, fueron aleatorizados para recibir 4 dosis de vacuna HiB a partir de los 3 meses de vida o una dosis inicial después de 24 meses de vida. Ratones NOD (propensos diabéticos no obesos) fueron inmunizados con la vacuna para determinar si la inmunización aumentó el riesgo de DMID.
- Los resultados muestran una asociación estadísticamente significativa entre la vacuna HiB y el incremento del riesgo de padecer DMID en un punto final prospectivo de 7 años en los niños finlandeses. En ratones NOD, la vacuna también inducía diabetes.
- Concluimos que la exposición a la inmunización HiB se asocia con un mayor riesgo de DMID. Los ratones NOD se pueden utilizar como modelo de diabetes inducida por la vacuna.

4. [Hernán MA, Jick SS, Olek MJ, Jick H. 2004. Recombinant hepatitis B vaccine and the risk of multiple sclerosis. *Neurology*. 63: 838-842]

Abstract—Background: A potential link between the recombinant hepatitis B vaccine and an increased risk of multiple sclerosis (MS) has been evaluated in several studies, but some of them have substantial methodologic limitations. **Methods:** The authors conducted a nested case-control study within the General Practice Research Database (GPRD) in the United Kingdom. The authors identified patients who had a first MS diagnosis recorded in the GPRD between January 1993 and December 2000. Cases were patients with a diagnosis of MS confirmed through examination of medical records, and with at least 3 years of continuous recording in the GPRD before their date of first symptoms (index date). Up to 10 controls per case were randomly selected, matched on age, sex, practice, and date of joining the practice. Information on receipt of immunizations was obtained from the computer records. **Results:** The analyses include 163 cases of MS and 1,604 controls. The OR of MS for vaccination within 3 years before the index date compared to no vaccination was 3.1 (95% CI 1.5, 6.3). No increased risk of MS was associated with tetanus and influenza vaccinations. **Conclusions:** These findings are consistent with the hypothesis that immunization with the recombinant hepatitis B vaccine is associated with an increased risk of MS, and challenge the idea that the relation between hepatitis B vaccination and risk of MS is well understood.

NEUROLOGY 2004;63:838–842

- Se ha evaluado un posible vínculo entre la vacuna contra la hepatitis B recombinante y un mayor riesgo de esclerosis múltiple (EM).
- Los autores identificaron pacientes en el Reino Unido que tuvieron un primer diagnóstico de EM registrado entre enero de 1993 y diciembre de 2000. La información de las inmunizaciones recibidas se obtuvo de los registros informáticos.
- Los análisis incluyen 163 casos de EM y 1.604 controles.
- Los resultados indican que la inmunización con la vacuna contra la hepatitis B recombinante se asocia con un aumento del riesgo de EM.

5. [Mikaeloff Y, Caridade G, Suissa S, Tardieu M. 2009. Hepatitis B vaccine and the risk of CNS inflammatory demyelination in childhood. *Neurology*. 72: 873-880]

ABSTRACT

Background: The risk of CNS inflammatory demyelination associated with hepatitis B (HB) vaccine is debated, with studies reporting conflicting findings.

Methods: We conducted a population-based case-control study where the cases were children with a first episode of acute CNS inflammatory demyelination in France (1994–2003). Each case was matched on age, sex, and geographic location to up to 12 controls, randomly selected from the general population. Information on vaccinations was confirmed by a copy of the vaccination certificate. The odds ratios (ORs) of CNS inflammatory demyelination associated with HB vaccination were estimated using conditional logistic regression.

Results: The rates of HB vaccination in the 3 years before the index date were 24.4% for the 349 cases and 27.3% for their 2,941 matched controls. HB vaccination within this period was not associated with an increase in the rate of CNS inflammatory demyelination (adjusted OR, 0.74; 0.54–1.02), neither >3 years nor as a function of the number of injections or brand type. When the analysis was restricted to subjects compliant with vaccination, HB vaccine exposure >3 years before index date was associated with an increased trend (1.50; 0.93–2.43), essentially from the Engerix B vaccine (1.74; 1.03–2.95). The OR was particularly elevated for this brand in patients with confirmed multiple sclerosis (2.77; 1.23–6.24).

Conclusions: Hepatitis B vaccination does not generally increase the risk of CNS inflammatory demyelination in childhood. However, the Engerix B vaccine appears to increase this risk, particularly for confirmed multiple sclerosis, in the longer term. Our results require confirmation in future studies.

Neurology® 2009;72:873–880

- El riesgo de desmielinización del SNC inflamatoria asociada a la vacuna contra la hepatitis B (HB) se debate con estudios que informan de resultados contradictorios.
- Se realizó un estudio de casos y controles de base poblacional, en el cual los casos eran niños con un primer episodio de desmielinización inflamatoria del SNC en Francia (1994-2003). Información sobre las vacunas fue confirmada por una copia de la vacunación certificada. Las odds ratio de desmielinización inflamatoria del SNC asociados con la vacunación HB se estimaron mediante la regresión logística condicional.
- Nuestros resultados indican que la vacuna HB generalmente no aumenta el riesgo de desmielinización inflamatoria del SNC en la infancia. Sin embargo, la vacuna Engerix B parece aumentar este riesgo, en particular para la esclerosis múltiple a largo plazo.
- Nuestros resultados requieren confirmación en estudios futuros.

6. [Jefferson T. 2006. Influenza vaccination: policy versus evidence. BMJ. 333:912-915]

-Este artículo es un análisis y no incluye un *abstract*. Los puntos clave del artículo son los siguientes:

- Cada año se pone un enorme esfuerzo en la producción de vacunas contra la gripe para ese año específico. Creemos que este esfuerzo no está justificado. La política pública recomienda el uso de vacunas antigripales inactivadas para prevenir brotes estacionales.
- Surgen tres problemas al intentar buscar evidencias sólidas:
 - 1) Hay una fuerte dependencia en estudios no aleatorios, principalmente de tipo cohorte, especialmente en ancianos (sesgo de selección)
 - 2) O bien la ausencia de pruebas o la falta de pruebas convincentes sobre la mayor parte de los efectos en el centro de los objetivos de la campaña de vacunación (en niños menores de 2 años, las vacunas inactivadas dieron los mismos resultados que el placebo y en adultos menores de 65 años no afectó la duración de hospitalización ni el tiempo de trabajo).
 - 3) El reducido y heterogéneo conjunto de datos sobre la seguridad de las vacunas inactivadas, lo cual es sorprendente dado su largo y extenso uso. La Cochrane encuentra solo un ensayo antiguo con datos de 35 participantes de 12-18 meses de edad.
- La gran brecha entre la política y los que nos dicen los datos es sorprendente. Las razones por las cuales existe esta brecha no están muy claras pero dado los enormes recursos involucrados, una re-evaluación debe ser emprendida con urgencia.

7. [Yoshida H, Horie H, Matsuura K, Miyamura T. 2000. Characterisation of vaccine-derived polioviruses isolated from sewage and river water in Japan. Lancet. 356: 1461-1463]

Background A nucleotide change from U to C at position 472 in the 5' non-coding region of the type 3 poliovirus is associated with increased neurovirulence. Moreover, the proportion of type 3 polioviruses containing this mutation (472-C revertants) correlates with the neurovirulence of a particular sample. We used mutant analysis by PCR and restriction-enzyme cleavage (MAPREC) to estimate the neurovirulence of environmental samples obtained from Toyama prefecture, Japan.

Methods Sewage and river water were collected between October, 1993, and September, 1995, and concentrated samples were inoculated into three different cell types. Isolated type 3 viruses were analysed to determine whether they were derived from the live oral poliovirus vaccine strain; they were then tested for neurovirulence by MAPREC.

Results 29 type 3 strains were isolated—all of which were vaccine-derived. 16 (55%) comprised between 2% and 91% 472-C revertants by MAPREC and were expected to have high neurovirulence. The remaining strains included less than 0.25% revertants, and were regarded as attenuated viruses. Both types were isolated about 3 months after routine oral poliovirus vaccine administrations in May and October. Three strains isolated from river water were of the virulent type.

Interpretation Our results emphasise that there is an environmental risk of vaccine-associated paralytic poliomyelitis as long as live oral poliovirus vaccine is not replaced by inactivated polio vaccine.

- Un cambio de nucleótido de U a C en la posición 472 en la región no codificante 5' del poliovirus tipo 3 es asociado con un aumento de la neurovirulencia. Mediante un análisis PCR y MAPREC se estimó la neurovirulencia de las muestras ambientales obtenidas en la prefectura de Toyama, Japón.
- Los resultados mostraron que tres cepas aisladas a partir de agua de río eran del tipo virulento.
- Nuestros resultados enfatizan que existe un riesgo ambiental de la poliomiелitis parálitica asociada a la vacuna siempre y cuando la vacuna antipoliomiелítica oral en vivo no sea sustituida por la vacuna de la polio inactivada.
- Dado que hay pocas posibilidades de que los individuos entren en contacto directo con las aguas negras, el riesgo de infección por esta ruta es muy baja. Sin embargo, el acceso al río es fácil para muchos individuos y los que son susceptibles deben ser considerados por tener un mayor riesgo de infección por el agua del río. La vacuna contra la poliomiелitis está mutando, ocasionando cepas virulentas.

8. [Geier MR, Geier DA, Zahalsky AC. 2003. Influenza vaccination and Guillain Barre syndrome. Clinical Immunology. 107: 116-121]

Abstract

Acute and severe Guillain Barre Syndrome (GBS) cases reported following influenza vaccine to the Vaccine Adverse Events Reporting System (VAERS) database from 1991 through 1999 were examined. Endotoxin concentrations were measured using the *Limulus* amoebocyte lysate assay in influenza vaccines. There were a total of 382 cases of GBS reported to the VAERS database following influenza vaccination (male/female ratio, 1.2). The median onset of GBS following influenza vaccine was 12 days (interquartile range, 7 days to 21 days). There was an increased risk of acute GBS (relative risk, 4.3; 95% confidence interval, 3.0 to 6.4) and severe GBS (relative risk, 8.5; 95% confidence interval, 3.7 to 18.9) in comparison to an adult tetanus-diphtheria (Td) vaccine control group. There were maximums in the incidence of GBS following influenza vaccine that occurred approximately every third year (1993, 1996, and 1998) and statistically significant variation in the incidence of GBS among different influenza manufacturers. Influenza vaccines contained from a 125- to a 1250-fold increase in endotoxin concentrations in comparison to an adult Td vaccine control and endotoxin concentrations varied up to 10-fold among different lots and manufacturers of influenza vaccine. The biologic mechanism for GBS following influenza vaccine may involve the synergistic effects of endotoxin and vaccine-induced autoimmunity. There were minimal potential reporting biases in the data reported to the VAERS database in this study. Patients should make an informed consent decision on whether to take this optional vaccine based upon its safety and efficacy and physicians should vigilantly report GBS following influenza vaccination to the VAERS in the United States so that continued evaluation of the safety of influenza vaccine may be undertaken.

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- Se examinaron los casos agudos y graves del síndrome de Guillain-Barré reportados después de la administración de la vacuna contra la influenza entre 1991-1999. Se midió también la concentración de endotoxina en las vacunas. La media del inicio del síndrome después de la vacuna fue de 12 días.
- En comparación con adultos que recibieron la vacuna contra el tétanos-difteria como control, se vio un mayor riesgo del síndrome de GB aguda (4,3) y grave (8,5)
- Las vacunas contra la influenza analizadas contenían 125-1250 veces mas concentración de endotoxina, en comparación con la concentración de endotoxina en la vacuna contra el tétanos-difteria adulta.
- El mecanismo biológico por el cual la vacuna puede causar el síndrome de GB puede involucrar los efectos sinérgicos de la endotoxina y la autoinmunidad inducida por la vacuna.
- Los pacientes deberían tomar una decisión informada, ya que esta vacuna es opcional y los médicos deben informar de este posible efecto de la vacuna y reportarla cuando la ven, para poder emprender una evaluación continua de la seguridad de la vacuna contra la influenza.

9. [Maglione MA, Das L, Raaen L, Smith A, Chari A, Newberry S, Shanman R, Perry T, Goetz MB, Gidengil C. 2014. Safety of Vaccines Used for Routine Immunization of US Children: A Systematic Review. Pediatrics. 134 (2): 325-337]

abstract Safety of Vaccines Used for Routine Immunization of US Children: A Systematic Review

BACKGROUND: Concerns about vaccine safety have led some parents to decline recommended vaccination of their children, leading to the resurgence of diseases. Reassurance of vaccine safety remains critical for population health. This study systematically reviewed the literature on the safety of routine vaccines recommended for children in the United States.

METHODS: Data sources included PubMed, Advisory Committee on Immunization Practices statements, package inserts, existing reviews, manufacturer information packets, and the 2011 Institute of Medicine consensus report on vaccine safety. We augmented the Institute of Medicine report with more recent studies and increased the scope to include more vaccines. Only studies that used active surveillance and had a control mechanism were included. Formulations not used in the United States were excluded. Adverse events and patient and vaccine characteristics were abstracted. Adverse event collection and reporting was evaluated by using the McHarm scale. We were unable to pool results. Strength of evidence was rated as high, moderate, low, or insufficient.

RESULTS: Of 20 478 titles identified, 67 were included. Strength of evidence was high for measles/mumps/rubella (MMR) vaccine and febrile seizures; the varicella vaccine was associated with complications in immunodeficient individuals. There is strong evidence that MMR vaccine is not associated with autism. There is moderate evidence that rotavirus vaccines are associated with intussusception. Limitations of the study include that the majority of studies did not investigate or identify risk factors for AEs; and the severity of AEs was inconsistently reported.

CONCLUSIONS: We found evidence that some vaccines are associated with serious AEs; however, these events are extremely rare and must be weighed against the protective benefits that vaccines provide. *Pediatrics* 2014;134:325-337

- Las preocupaciones sobre la seguridad de las vacunas han llevado a algunos padres a rechazar la vacunación recomendada de sus hijos, lo que lleva a la reaparición de enfermedades. La seguridad de las vacunas sigue siendo crítica para la salud de la población. Este estudio revisó sistemáticamente la literatura sobre la seguridad de las vacunas de rutina recomendadas para niños en los EEUU.

- De 20.478 artículos identificados, 67 fueron incluidos. Datos revelan que existe una asociación entre la vacuna del sarampión/paperas/ rubéola y convulsiones febriles; la vacuna contra la varicela se asoció con complicaciones en personas inmunodeficientes. Hay una fuerte evidencia de que la vacuna del sarampión/paperas/rubéola no esta asociada con el autismo. Hay pruebas moderadas de que las vacunas contra el rotavirus se asocian con la invaginación intestinal.

- Se encontró evidencia de que algunas vacunas están asociadas con eventos adversos graves. Sin embargo, estos acontecimientos son extremadamente raros y deben ser sopesados frente a los beneficios de protección que las vacunas proporcionan. Balance riesgo-beneficio.

10. ["Possible Side-effects from Vaccines". Centers for Disease Control and Prevention. 11 June 2015.] <http://www.cdc.gov/vaccines/vac-gen/side-effects.htm#mmr>

-Este enlace es para la página web de la CDC. Muestra una lista de las vacunas disponibles y sus posibles efectos adversos documentados.

11. [Klein NP et.al. 2010. Measles-Mumps-Rubella-Varicella Combination Vaccine and the Risk of Febrile Seizures. Pediatrics. 126(1): 1-8] <http://pediatrics.aappublications.org/content/126/1/e1.short>

ABSTRACT

OBJECTIVE: In February 2008, we alerted the Advisory Committee on Immunization Practices to preliminary evidence of a twofold increased risk of febrile seizures after the combination measles-mumps-rubella-varicella (MMRV) vaccine when compared with separate measles-mumps-rubella (MMR) and varicella vaccines. Now with data on twice as many vaccine recipients, our goal was to reexamine seizure risk after MMRV vaccine.

METHODS: Using 2000-2008 Vaccine Safety Datalink data, we assessed seizures and fever visits among children aged 12 to 23 months after MMRV and separate MMR + varicella vaccines. We compared seizure risk after MMRV vaccine to that after MMR + varicella vaccines by using Poisson regression as well as with supplementary regressions that incorporated chart-review results and self-controlled analyses.

RESULTS: MMRV vaccine recipients (83 107) were compared with recipients of MMR + varicella vaccines (376 354). Seizure and fever significantly clustered 7 to 10 days after vaccination with all measles-containing vaccines but not after varicella vaccination alone. Seizure risk during days 7 to 10 was higher after MMRV than after MMR + varicella vaccination (relative risk: 1.98 [95% confidence interval: 1.43-2.73]). Supplementary analyses yielded similar results. The excess risk for febrile seizures 7 to 10 days after MMRV compared with separate MMR + varicella vaccination was 4.3 per 10 000 doses (95% confidence interval: 2.6-5.6).

CONCLUSIONS: Among 12- to 23-month-olds who received their first dose of measles-containing vaccine, fever and seizure were elevated 7 to 10 days after vaccination. Vaccination with MMRV results in 1 additional febrile seizure for every 2300 doses given instead of separate MMR + varicella vaccines. Providers who recommend MMRV should communicate to parents that it increases the risk of fever and seizure over that already associated with measles-containing vaccines.

- En febrero de 2008 alertamos al comité asesor sobre prácticas de inmunización debido a la evidencia preliminar de un doble riesgo de convulsiones febriles después de la combinación de la vacuna del sarampión/paperas/rubéola/varicela en comparación con distintos regímenes de vacunación.

- Datos utilizados del 2000-2008 de Vacunas Datalink fueron evaluados, observando las convulsiones febriles vistas en niños de 12-23 meses después de sus vacunaciones combinadas y separadas, comparando el riesgo de convulsiones, utilizando la regresión de Poisson.

-Se observaron convulsiones y estados febriles 7-10 días después de la vacunación combinada, pero no después de la vacunación contra la varicela solo. El riesgo de sufrir convulsiones durante los días 7-10 fue mayor después de la vacuna cuádruple (4,3 por cada 10.000 dosis) que la triple + varicela (1,98 por cada 10.000 dosis).

12a. [Kawahara M. 2005. Effects of aluminum on the nervous system and its posible link with neurodegenerative diseases. Journal of Alzheimer's Disease. 8(2): 171-182] <http://europepmc.org/abstract/med/16308486>

Aluminum is environmentally abundant, but not an essential element. Aluminum has been associated with several neurodegenerative diseases, such as dialysis encephalopathy, amyotrophic lateral sclerosis and Parkinsonism dementia in the Kii peninsula and Guam, and in particular, Alzheimer's disease. Although this association remains controversial, there is increasing evidence which suggests the implication of metal homeostasis in the pathogenesis of Alzheimer's disease. Aluminum, zinc, copper, and iron cause the conformational changes of Alzheimer's amyloid-beta protein. Al causes the accumulation of tau protein and amyloid-beta protein in experimental animals. Aluminum induces neuronal apoptosis *in vivo* as well as *in vitro*. Furthermore, a relationship between aluminum and the iron-homeostasis or calcium-homeostasis has been suggested. Based on these findings, the characteristics of aluminum neurotoxicity are reviewed, and the potential link between aluminum and neurodegenerative diseases is reconsidered.

-Cada vez hay más evidencia que sugiere la implicación de la homeostasis del aluminio en la patogénesis de la enfermedad de Alzheimer.

- El aluminio y otros metales causan los cambios conformacionales de la proteína beta-amiloide. Causa la acumulación de la proteína tau y la proteína beta-amiloide en animales experimentales. Induce apoptosis neuronal *in vivo* así como *in vitro*.

12b. [Shaw CA, Tomljenovic L. 2013. Aluminum in the central nervous system (CNS): toxicity in humans and animals, vaccine adjuvants, and autoimmunity. Immunol Res. 56: 304-316]

Abstract We have examined the neurotoxicity of aluminum in humans and animals under various conditions, following different routes of administration, and provide an overview of the various associated disease states. The literature demonstrates clearly negative impacts of aluminum on the nervous system across the age span. In adults, aluminum exposure can lead to apparently age-related neurological deficits resembling Alzheimer's and has been linked to this disease and to the Guamanian variant, ALS-PDC. Similar outcomes have been found in animal models. In addition, injection of aluminum adjuvants in an attempt to model Gulf War syndrome and associated neurological deficits leads to an ALS phenotype in young male mice. In young children, a highly significant correlation exists between the number of pediatric aluminum-adjuvanted vaccines administered and the rate of autism spectrum disorders. Many of the features of aluminum-induced neurotoxicity may arise, in part, from autoimmune reactions, as part of the ASIA syndrome.

-Se examina la neurotoxicidad del aluminio en seres humanos y animales. La literatura claramente demuestra los impactos negativos del aluminio sobre el sistema nervioso central a través de un rango de edad. En adultos, la exposición al aluminio puede culminar en déficits neurológicos aparentemente relacionados con el envejecimiento como la enfermedad de Alzheimer (variante de Guam, ALS-PDC).

-Además, la inyección de vacunas con aluminio como adyuvante se ha utilizado para intentar reproducir el síndrome de la Guerra del Golfo (déficits neurológicos) en ratones.

-En niños, existe una correlación altamente significativa entre el número de vacunas pediátricas con aluminio como adyuvante y la tasa de los trastornos del espectro autista.

-Muchas de las características de la toxicidad inducida por aluminio pueden dar lugar incluso a reacciones autoinmunes, como parte del síndrome de ASIA.

12c. [Jaishankar M, Tseten T, Anbalagan N, Mathew BB, Beeregowda N. 2014. Toxicity, mechanism and health effects of some heavy metals. *Interdiscip Toxicol.* 7(2): 60-72]

-Este artículo explora los diferentes efectos citotóxicos de metales y su mecanismo de acción. Aquí únicamente incluyo el apartado de mecanismo de acción de citotoxicidad del aluminio.

Mechanism of aluminium toxicity

Aluminium interferes with most physical and cellular processes. The exact mechanism of absorption of aluminium by the gastrointestinal tract is not understood completely. Based on literature surveys, it is difficult to give a proper time period for aluminium toxicity since some symptoms of aluminium toxicity can be detected in seconds and others in minutes after exposure to aluminium (WHO, 1997). Aluminium toxicity probably results from the interaction between aluminium and plasma membrane, apoplasmic and symplasmic targets (Kochian *et al.*, 2005). In humans Mg^{2+} and Fe^{3+} are replaced by Al^{3+} , which causes many disturbances associated with intercellular communication, cellular growth and secretory functions. The changes that are evoked in neurons by aluminium are similar to the degenerative lesions observed in Alzheimer patients. The greatest complications of aluminium toxicity are neurotoxicity effects such as neuronal atrophy in the locus ceruleus, substantia nigra and striatum (Filiz & Meral, 2007).

- El aluminio interfiere con la mayoría procesos físicos y celulares.

-Se desconoce exactamente el mecanismo de absorción de aluminio en el tracto gastrointestinal.

-Basándose en la literatura disponible, es difícil citar cuando se pueden esperar síntomas causados por la toxicidad del aluminio.

-El mecanismo de toxicidad probablemente es el resultante de la interacción entre el aluminio y la membrana plasmática.

-En los seres humanos, Mg^{2+} Fe^{3+} se sustituyen por Al^{3+} lo cual causa muchos trastornos asociados con la comunicación intercelular, el crecimiento celular y las funciones secretoras.

-Los cambios que se evocan en las neuronas por el aluminio son similares a las lesiones degenerativas que se observan en pacientes con Alzheimer.

-Se ha observado que la neurotoxicidad del aluminio puede culminar en atrofia neuronal en el locus ceruleus, sustancia negra y el estriado.

12d. [Guillard O, Fauconneau B, Pineau A, Marraud A, Bellocq JP, Chenard MP. 2012. Aluminium overload after 5 years in skin biopsy following post-vaccination with subcutaneous pseudolymphoma. Journal of Trace Elements in Medicine and Biology. 26(4): 291-293]

ABSTRACT

Aluminium hydroxide is used as an effective adjuvant in a wide range of vaccines for enhancing immune response to the antigen. The pathogenic role of aluminium hydroxide is now recognized by the presence of chronic fatigue syndrome, macrophagic myofasciitis and subcutaneous pseudolymphoma, linked to intramuscular injection of aluminium hydroxide-containing vaccines. The aim of this study is to verify if the subcutaneous pseudolymphoma observed in this patient in the site of vaccine injection is linked to an aluminium overload. Many years after vaccination, a subcutaneous nodule was discovered in a 45-year-old woman with subcutaneous pseudolymphoma. In skin biopsy at the injection site for vaccines, aluminium (Al) deposits are assessed by Morin stain and quantification of Al is performed by Zeeman Electrothermal Atomic Absorption Spectrophotometry. Morin stain shows Al deposits in the macrophages, and Al assays (in $\mu\text{g/g}$, dry weight) were 768.10 ± 18 for the patient compared with the two control patients, 5.61 ± 0.59 and 9.13 ± 0.057 . Given the pathology of this patient and the high Al concentration in skin biopsy, the authors wish to draw attention when using the Al salts known to be particularly effective as adjuvants in single or repeated vaccinations. The possible release of Al may induce other pathologies ascribed to the well-known toxicity of this metal.

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- El hidróxido de aluminio se utiliza como adyuvante en una amplia gama de vacunas para mejorar la respuesta inmune al antígeno. El papel patógeno del aluminio es ahora reconocido por la presencia de síndrome de fatiga crónica, miofascitis macrofágica y pseudolinfoma subcutáneo, vinculados a la inyección intramuscular de vacunas que contienen este metal.

-El objetivo de este estudio era verificar si el pseudolinfoma subcutáneo observado en nuestro paciente en el sitio de inyección de la vacuna está ligado a una sobrecarga de aluminio. Muchos años después de la vacunación, se observa un nódulo subcutáneo en una mujer de 45 años. En la biopsia de la piel en el sitio de la inyección de vacunas, se encontraron depósitos de alta concentración aluminio. Los autores quieren llamar la atención al peligro de utilizar sales de aluminio en vacunas.

13. [Barlow WE et.al. 2001. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. New England Journal of Medicine. 345 (9): 656-661] <http://www.nejm.org/doi/pdf/10.1056/NEJMoa003077>

ABSTRACT

Background The administration of the diphtheria and tetanus toxoids and whole-cell pertussis (DTP) vaccine and measles, mumps, and rubella (MMR) vaccine has been associated with seizures. We studied the relation between these vaccinations and the risk of a first seizure, subsequent seizures, and neurodevelopmental disability in children.

Methods This cohort study was conducted at four large health maintenance organizations and included reviews of the medical records of children with seizures. We calculated the relative risks of febrile and nonfebrile seizures among 679,942 children after 340,386 vaccinations with DTP vaccine, 137,457 vaccinations with MMR vaccine, or no recent vaccination. Children who had febrile seizures after vaccination were followed to identify the risk of subsequent seizures and other neurologic disabilities.

Results Receipt of DTP vaccine was associated with an increased risk of febrile seizures only on the day of vaccination (adjusted relative risk, 5.70; 95 percent confidence interval, 1.98 to 16.42). Receipt of MMR vaccine was associated with an increased risk of febrile seizures 8 to 14 days after vaccination (relative risk, 2.83; 95 percent confidence interval, 1.44 to 5.55). Neither vaccination was associated with an increased risk of nonfebrile seizures. The number of febrile seizures attributable to the administration of DTP and MMR vaccines was estimated to be 6 to 9 and 25 to 34 per 100,000 children, respectively. As compared with other children with febrile seizures that were not associated with vaccination, the children who had febrile seizures after vaccination were not found to be at higher risk for subsequent seizures or neurodevelopmental disabilities.

Conclusions There are significantly elevated risks of febrile seizures after receipt of DTP vaccine or MMR vaccine, but these risks do not appear to be associated with any long-term, adverse consequences. (N Engl J Med 2001;345:656-61.)

-La administración de los toxoides diftéricos y tetánicos y tos ferina (DTP) y del sarampión las paperas y la rubéola (MMR) se ha asociado con convulsiones.

-Se estudió la relación entre estas vacunas y el riesgo de una primera crisis, convulsiones posteriores y trastornos del desarrollo neural de los niños.

-Existen riesgos significativamente elevados de convulsiones febriles después de la recepción de la vacuna DTP o vacuna triple vírica, pero estos riesgos no parecen estar asociados con cualquier consecuencia adversa a largo plazo.

14. [Song JY, Cheong HJ, Hwang IS, Choi WS, Jo YM, Park DW, Cho GJ, Hwang TG, Kim WJ. 2010. Long-term immunogenicity of influenza vaccine among the elderly: Risk factors for poor immune response and persistence. *Vaccine*. 28: 3929-3935]

A B S T R A C T	
The elderly have been considered as the priority group for influenza vaccination, but their influenza vaccine-induced antibody was believed to decline more rapidly. Long-term immunogenicity of the influenza vaccine among the elderly was evaluated as compared to young adults. Serum hemagglutinin inhibition (HI) titers were determined at pre- and post-vaccination periods (at 1, 6, and 12 months after vaccination). Of the 1018 subjects, 716 (70.3%) were followed up during a 12-month period. Seroprotection rates at 1 month post-vaccination ranged from 70.1% to 90.3% depending on the age group and influenza vaccine virus strain. At 6 months post-vaccination, seroprotection rates for all three strains had declined significantly in adults ≥ 65 years ($P < 0.01$), but still met the EMEA criteria. Low pre-vaccination HI titer ($< 1:40$) and advanced age were associated with early decline of HI titers, falling below seroprotective levels around 6 months after vaccination.	
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- Los ancianos han sido considerados como el grupo prioritario para la vacunación contra la gripe, pero sus anticuerpos inducidos por la vacuna disminuyen más rápidamente.
- Se evaluó la inmunogenicidad a largo plazo de la vacuna antigripal en los ancianos, en comparación con adultos jóvenes.
- Las tasas de seroprotección disminuyeron significativamente en adultos > 65 años, cayendo por debajo de niveles seroprotectores alrededor de 6 meses después de la vacunación.

15. Geier DA, Geier MR. 2006. An assessment of downward trends in neurodevelopmental disorders in the United States following removal of thimerosal from childhood vaccines. *Med Sci Monit*. 12(6): 231-239]

Summary	
Background:	The US is in the midst of an epidemic of neurodevelopmental disorders (NDs). Thimerosal is an ethylmercury-containing compound added to some childhood vaccines. Several previous epidemiological studies conducted in the US have associated Thimerosal-containing vaccine (TCV) administration with NDs.
Material/Methods:	An ecological study was undertaken to evaluate NDs reported to the Vaccine Adverse Event Reporting System (VAERS) from 1991 through 2004 by date of receipt and by date of vaccine administration. The NDs examined included autism, mental retardation, and speech disorders. Statistical trend analysis was employed to evaluate the effects of removal of Thimerosal on the proportion of NDs reported to VAERS.
Results:	There was a peak in the proportion of ND reports received by VAERS in 2001–2002 and in the proportion of ND reports by date of vaccine administration in 1998. There were significant reductions in the proportion of NDs reported to VAERS as Thimerosal was begun to be removed from childhood vaccines in the US from mid-1999 onwards.
Conclusions:	The present study provides the first epidemiological evidence showing that as Thimerosal was removed from childhood vaccines, the number of NDs has decreased in the US. The analysis techniques utilized attempted to minimize chance or bias/confounding. Additional research should be conducted to further evaluate the relationship between TCVs and NDs. This is especially true because the handling of vaccine safety data from the National Immunization Program of the CDC has been called into question by the Institute of Medicine of the National Academy of Sciences in 2005.

- Los EEUU está en medio de una epidemia de trastornos del neurodesarrollo. El timerosal es un compuesto que contiene etilmercurio agregado para algunas vacunas infantiles. Se realizó un estudio ecológico para evaluar la incidencia de enfermedades del neurodesarrollo con la eliminación de timerosal en las vacunas.
- Los resultados muestran una reducción significativa en la proporción de enfermedades del neurodesarrollo reportadas mientras que se retiró el timerosal.

16. [Molina V, Shoenfeld Y. 2005. Infection, vaccines and other environmental triggers of autoimmunity. *Autoimmunity*. 38(3): 235-245]

Abstract	
The etiology of autoimmune diseases is still not clear but genetic, immunological, hormonal and environmental factors are considered to be important triggers. Most often autoimmunity is not followed by clinical symptoms unless an additional event such as an environmental factor favors an overt expression. Many environmental factors are known to affect the immune system and may play a role as triggers of the autoimmune mosaic. Infections: bacterial, viral and parasitic infections are known to induce and exacerbate autoimmune diseases, mainly by the mechanism of molecular mimicry. This was studied for some syndromes as for the association between SLE and EBV infection, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection and more. Vaccines, in several reports were found to be temporally followed by a new onset of autoimmune diseases. The same mechanisms that act in infectious invasion of the host, apply equally to the host response to vaccination. It has been accepted for diphtheria and tetanus toxoid, polio and measles vaccines and GBS. Also this theory has been accepted for MMR vaccination and development of autoimmune thrombocytopenia, MS has been associated with HBV vaccination. Occupational and other chemical exposures are considered as triggers for autoimmunity. A debate still exists about the role of silicone implants in induction of scleroderma like disease. Not only foreign chemicals and agents have been associated with induction of autoimmunity, but also an intrinsic hormonal exposure, such as estrogens. This might explain the sexual dimorphism in autoimmunity. Better understanding of these environmental risk factors will likely lead to explanation of the mechanisms of onset and progression of autoimmune diseases and may lead to effective preventive involvement in specific high-risk groups. So by diagnosing a new patient with autoimmune disease a wide anamnesis work should be done.	

-Muchos factores ambientales afectan el sistema inmunológico y pueden jugar un papel como desencadenantes. Infecciones bacterianas, virales y parasitarias pueden inducir y exacerbar enfermedades autoinmunes por el mecanismo de mimetismo molecular. También se han encontrado vacunas en varios informes que fueron seguidas de enfermedades autoinmunes. Los mismos mecanismos que actúan en la invasión infecciosa del huésped se aplican igualmente a la respuesta del huésped a la vacunación.

17. [Tomljenovic L, Wilyman J, Vanamee E, Bark T, Shaw CA. 2013. HPV vaccines and cancer prevention, science versus activism. Infectious Agents and Cancer. 8:6]

Abstract

The rationale behind current worldwide human papilloma virus (HPV) vaccination programs starts from two basic premises, 1) that HPV vaccines will prevent cervical cancers and save lives and, 2) have no risk of serious side effects. Therefore, efforts should be made to get as many pre-adolescent girls vaccinated in order to decrease the burden of cervical cancer. Careful analysis of HPV vaccine pre- and post-licensure data shows however that both of these premises are at odds with factual evidence and are largely derived from significant misinterpretation of available data.

-El fundamento de los programas de vacunación actuales contra el VPH se inicia a partir de dos premisas, 1) que las vacunas contra el VPH evitarán cánceres de cuello uterino y salvará vidas y, 2) no tienen riesgos graves o efectos secundarios. Un análisis cuidadoso muestra, sin embargo, que estas premisas están en desacuerdo con pruebas científicas y se derivan en gran parte de la mala interpretación de la información disponible.

El autor añade una serie de preguntas que se deberían hacer aquellos que deseen promover la vacuna, incluyendo:

- No se han demostrado que las vacunas contra el VPH ayuden a prevenir el cáncer de cuello uterino. Así pues, ¿por qué se promueve su uso?
- Si la mayoría de las infecciones por VPH y una gran proporción de lesiones pre-cancerosas aclaran espontáneamente sin tratamiento médico y por lo tanto no son una indicación fiable de cáncer, ¿cómo se pueden atribuir los indicadores de casos de cáncer de cuello uterino a la vacuna?
- ¿Por qué no se informa a las mujeres de que en algunas circunstancias, la vacunación contra el VPH puede acelerar la progresión de anomalías cervicales?

18. [McKinlay JB, McKinlay SM. 1977. The questionable contribution of medical measures to the decline of mortality in the United States in the twentieth century. Millbank Mem Fund Q Health Soc. 55(3): 405-428]

-Este artículo concluye lo siguiente:

In general, medical measures (both chemotherapeutic and prophylactic) appear to have contributed little to the overall decline in mortality in the United States since about 1900—having in many instances been introduced several decades after a marked decline had already set in and having no detectable influence in most instances. More specifically, with reference to those five conditions (influenza, pneumonia, diphtheria, whooping cough, and poliomyelitis) for which the decline in mortality appears substantial after the point of intervention—and on the unlikely assumption that all of this decline is attributable to the intervention—it is estimated that at most 3.5 percent of the total decline in mortality since 1900 could be ascribed to medical measures introduced for the diseases considered here.

-Por regla general, las intervenciones médicas (quimioterapéuticas y profilácticas) no parecen haber contribuido al declive en mortalidad infantil en los EEUU desde alrededor de 1900.

-En muchas ocasiones, estas intervenciones médicas se introdujeron varias décadas después de que la enfermedad empezara a remitir, teniendo poca influencia en muchas instancias.

-En las condiciones como la influenza, neumonía, difteria, tos ferina y poliomielitis, el declive en mortalidad aparece sustancial después de una intervención pero no se puede asumir que todo el declive se puede atribuir a la intervención.

-Se estima que como mucho, un 3,5% del declive total en la mortalidad desde 1900 se puede adscribir a intervenciones médicas introducidas para las enfermedades mencionadas anteriormente.

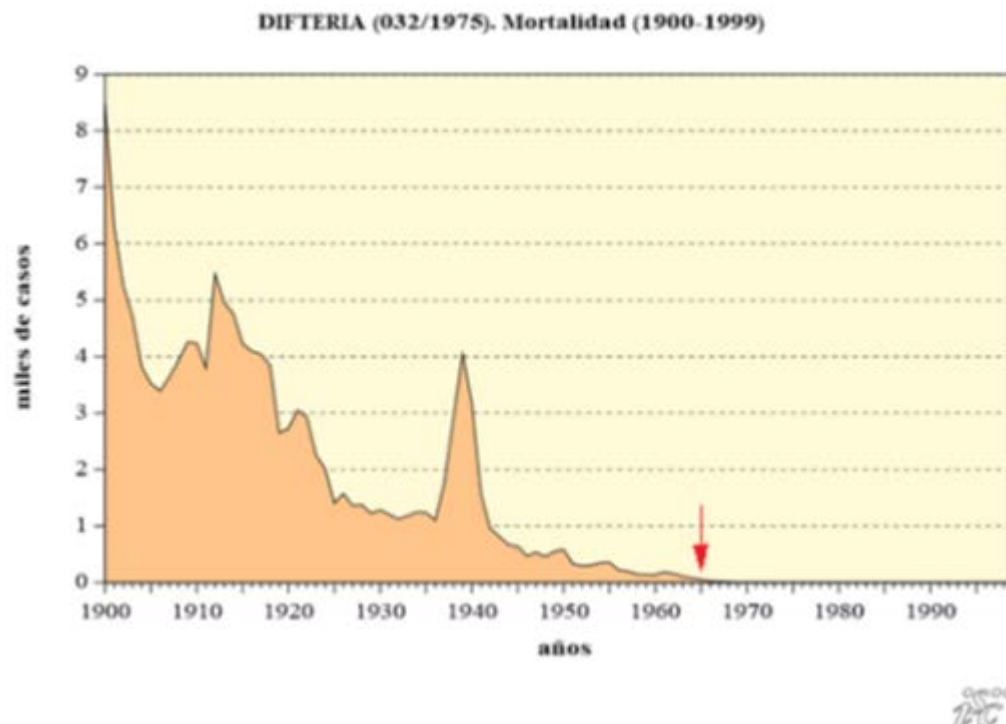
-Sugieren que la mejora del saneamiento, las condiciones de vida y menos hacinamiento contribuyeron de forma mayoritaria al declive en mortalidad, no las intervenciones médicas (vacunas).

19.<http://gesdoc.isciii.es/gesdoccontroller?action=download&id=19/10/2012-3c0cfd4ca3>

En este enlace al Gestor Documental del Instituto de Salud Carlos III, donde aparece el trabajo de investigación “Análisis de la sanidad en España siglo xx”, en su página 116, se encuentran tablas de la evolución del descenso de los casos de muerte por difteria en España desde 1900.

DIFTERIA (032/1975). Mortalidad (1900-1999) y Tasas/100.000 h.

Años	N.º	Tasa	Años	N.º	Tasa	Años	N.º	Tasa	Años	N.º	Tasa	Años	N.º	Tasa
1900	8.489	45,5	1920	2.732	12,8	1940	3.169	12,3	1960	139	0,5	1980	0	0
1901	6.299	37,3	1921	3.052	14,2	1941	1.563	6	1961	190	0,6	1981	0	0
1902	5.247	27,9	1922	2.937	13,6	1942	956	3,7	1962	156	0,5	1982	0	0
1903	4.721	25,1	1923	2.260	10,3	1943	816	3,1	1963	110	0,4	1983	1	X
1904	3.823	20,1	1924	2.009	9,1	1944	669	2,5	1964	81	0,2	1984	1	X
1905	3.524	18,4	1925	1.407	6,3	1945	642	2,4	1965	56	0,2	1985	0	0
1906	3.390	17,5	1926	1.576	7	1946	472	1,7	1966	24	0,1	1986	0	0
1907	3.634	18,7	1927	1.363	6	1947	533	2	1967	18	X	1987	1	X
1908	3.926	20	1928	1.377	6	1948	460	1,7	1968	14	X	1988	0	0
1909	4.256	21,6	1929	1.225	5,3	1949	550	2	1969	7	X	1989	0	0
1910	4.239	21,3	1930	1.288	5,4	1950	587	2,1	1970	5	X	1990	0	0
1911	3.799	19	1931	1.203	5,1	1951	333	1,2	1971	6	X	1991	0	0
1912	5.465	27,1	1932	1.123	4,7	1952	297	1	1972	6	X	1992	0	0
1913	4.956	24,4	1933	1.181	4,9	1953	305	1,1	1973	3	X	1993	0	0
1914	4.756	23,3	1934	1.250	5,1	1954	352	1,2	1974	4	X	1994	0	0
1915	4.231	20,6	1935	1.238	5	1955	363	1,2	1975	1	X	1995	0	0
1916	4.097	19,8	1936	1.103	4,4	1956	224	0,8	1976	4	X	1996	0	0
1917	4.044	19,4	1937	1.773	7,1	1957	199	0,7	1977	3	X	1997	0	0
1918	3.844	18,3	1938	2.930	11,6	1958	149	0,5	1978	2	X	1998		
1919	2.650	12,5	1939	4.058	15,9	1959	141	0,1	1979	1	X	1999		



En este último gráfico hemos marcado con una flecha roja el año de introducción (1965) de la vacunación masiva de la difteria según el mismo documento.

20. [Eloe-Fadrosch EA, McArthur MA, Seekatz AM, Drabek EF, Rasko DA, Szein MB, Fraser CM. 2013. Impact of Oral Typhoid Vaccination on the Human Gut Microbiota and Correlations with *S. Typhi*-Specific Immunological Responses. PLOS one. 8(4): e2026]

Abstract

The resident microbial consortia of the human gastrointestinal tract play an integral role in modulating immune responses both locally and systemically. However, detailed information regarding the effector immune responses after vaccine administration in relation to the gastrointestinal microbiota is absent. In this study, the licensed oral live-attenuated typhoid vaccine Ty21a was administered in a clinical study to investigate whether oral immunization resulted in alterations of the microbiota and to identify whether a given microbiota composition, or subsets of the community, are associated with defined *S. Typhi*-specific immunological responses. The fecal microbiota composition and temporal dynamics were characterized using bacterial 16S rRNA pyrosequencing from individuals who were either immunized with the Ty21a typhoid vaccine ($n=13$) or served as unvaccinated controls ($n=4$). The analysis revealed considerable inter- and intra-individual variability, yet no discernible perturbations of the bacterial assemblage related to vaccine administration were observed. *S. Typhi*-specific cell mediated immune (CMI) responses were evaluated by measurement of intracellular cytokine production using multiparametric flow cytometry, and humoral responses were evaluated by measurement of serum anti-LPS IgA and IgG titers. Volunteers were categorized according to the kinetics and magnitude of their responses. While differences in microbial composition, diversity, or temporal stability were not observed among individuals able to mount a positive humoral response, individuals displaying multiphasic CMI responses harbored more diverse, complex communities. In line with this preliminary observation, over two hundred operational taxonomic units (OTUs) were found to differentiate multiphasic and late CMI responders, the vast majority of which classified within the order Clostridiales. These results provide an unprecedented view into the dramatic temporal heterogeneity of both the gut microbiota and host immune responses.

-El ecosistema bacteriano intestinal juega un papel integral en la modulación de la respuesta inmune tanto a nivel local como sistemático. Se necesita investigar detalladamente las respuestas inmunes efectoras después de la administración de una vacuna, en relación con la microbiota gastrointestinal.

-En este estudio, la fiebre tifoidea atenuada en vivo administrada por vía oral como vacuna se administró para investigar si la inmunización oral resultó en alteraciones de la microbiota y para investigar si ciertas composiciones o subconjuntos de microbiota están asociados con distintas respuestas inmunológicas a *S. Typhi*.

-El análisis reveló una variabilidad considerable en sentido inter e intraindividual. Los voluntarios fueron clasificados de acuerdo con la cinética y la magnitud de sus respuestas. Los individuos que exhibían respuestas multifásicas y respuestas celulares inmunológicas tardías albergaban comunidades más diversas y complejas.

-Estos resultados proporcionan una visión sin precedentes de la heterogeneidad temporal dramática tanto de la microbiota intestinal y respuestas inmunológicas después de una vacunación oral contra *S. Typhi*.

21. [Buttery JP, Riddell A, McVernon J, et al. 2005. Immunogenicity and Safety of a Combination Pneumococcal-Meningococcal Vaccine in Infants. JAMA. 293 (14): 1751-1758]

Context The success of conjugate vaccines in decreasing invasive disease due to *Streptococcus pneumoniae* and group C *Neisseria meningitidis* has placed pressure on crowded infant immunization schedules, making development of combination vaccines a priority.

Objective To determine the safety and immunogenicity of a combination 9-valent pneumococcal-group C meningococcal conjugate candidate vaccine (Pnc9-MenC) administered as part of the routine UK infant immunization schedule at ages 2, 3, and 4 months.

Design, Setting, and Participants Phase 2 randomized controlled trial conducted from August 2000 to January 2002 and enrolling 240 healthy infants aged 7 to 11 weeks from 2 UK centers, with home follow-up visits at ages 2, 3, 4, and 5 months.

Intervention Pnc9-MenC (n=120) or monovalent group C meningococcal conjugate vaccine (MenC) (n=120) administered in addition to routine immunizations (diphtheria and tetanus toxoids and whole-cell pertussis [DTwP], *Haemophilus influenzae* type b [Hib] polyribosylribitol phosphate-tetanus toxoid protein conjugate, oral polio vaccine).

Main Outcome Measures Group C meningococcal immunogenicity measured by serum bactericidal titer (SBT) 1 month following the third dose; rates of postimmunization reactions.

Results MenC component immunogenicity was reduced in the Pnc9-MenC vs the MenC group (geometric mean SBT, 179 [95% confidence interval (CI), 133-243] vs 808 [95% CI, 630-1037], respectively; $P<.001$). The proportion with group C meningococcal SBT greater than 1:8 was lower in the Pnc9-MenC vs the MenC group (95% vs 100%, $P=.05$). The geometric mean concentration of antibodies to concomitantly administered Hib vaccine was reduced in the Pnc9-MenC vs the MenC group (2.11 [95% CI, 1.57-2.84] $\mu\text{g/mL}$ vs 3.36 [95% CI, 2.57-4.39] $\mu\text{g/mL}$; $P=.02$), as were antibodies against diphtheria (0.74 [95% CI, 0.63-0.87] $\mu\text{g/mL}$ vs 1.47 [95% CI, 1.28-1.69] $\mu\text{g/mL}$; $P<.001$). Pnc9-MenC was immunogenic for each of 9 contained pneumococcal serotypes, with responses greater than 0.35 $\mu\text{g/mL}$ observed in more than 88% of infants. Increased irritability and decreased activity were observed after the third dose in the Pnc9-MenC group.

Conclusions Pnc9-MenC combination vaccine administered to infants at ages 2, 3, and 4 months demonstrated reduced group C meningococcal immunogenicity compared with MenC vaccine. The immunogenicity of concomitantly administered Hib and DTwP vaccines was also diminished. The Pnc9-MenC vaccine was safe and immunogenic for all contained pneumococcal serotypes. The reduced MenC immunogenicity may limit the development of the Pnc9-MenC vaccine.

-Las vacunas conjugadas han visto un éxito en la disminución de la enfermedad invasiva por *Streptococcus pneumoniae* y *Neisseria meningitidis* del grupo C. Esto ha supuesto una presión importante en los calendarios de vacunación infantiles, por lo que se está dando prioridad al desarrollo de vacunas combinadas.

-Nuestro objetivo era determinar la seguridad y la inmunogenicidad de la combinación de vacuna: neumocócica grupo 9 y antimeningocócica grupo C (Pnc9-MenC), administrado de manera rutinaria en el Reino Unido a niños de 2, 3, y 4 meses.

-Los resultados demuestran que la vacuna combinada Pnc9-MenC administrada a bebés a los 2, 3 y 4 meses redujo la inmunogenicidad meningocócica en comparación con la vacuna MenC única. La inmunogenicidad de *Haemophilus influenzae* tipo B se administra normalmente concomitantemente con pertussis, hecho que también disminuye la inmunogenicidad.

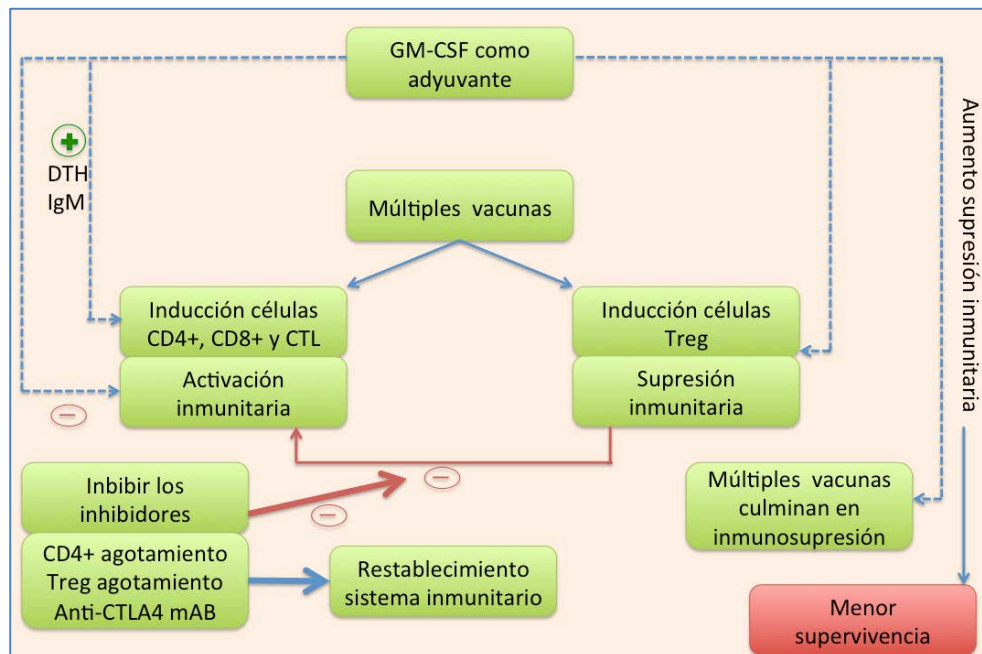
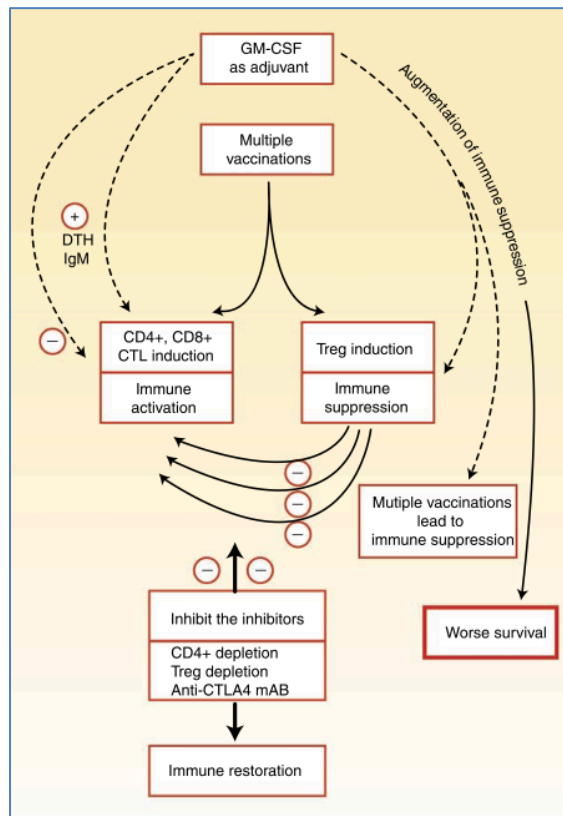
Al final del artículo, los autores comentan que sus resultados ponen de manifiesto la imprevisibilidad de las reacciones inmunes individuales a cada antígeno de una vacuna combinada. Subrayan la importancia de evaluar la inmunogenicidad de toda la vacuna en ensayos previos a la vacunación. Concluyen que la vacuna combinada Pnc9-MenC no es un sustituto adecuado para las vacunas individuales correspondientes.

22. [Eggermont AMM. 2009. Immunostimulation Versus Immunosuppression after Multiple Vaccinations: the Woes of Therapeutic Vaccine Development. Clin Cancer Res. 15(22): 6745-6747]

Three articles in this issue of *Clinical Cancer Research* show how multiple vaccinations can lead to immunosuppression. Moreover, two studies in patients show that granulocyte macrophage colony-stimulating factor (GM-CSF) as an adjuvant immunostimulant to different kind of vaccines can lead to adverse outcome in terms of relapse-free and overall survival. Modulation of regulatory T-cell activity may be required to overcome this outcome and may be crucial for the successful development of therapeutic vaccines. (Clin Cancer Res 2009;15(22):6745-7)

-Ya se han publicado tres artículos de este número de la revista *Clinical Cancer Research* que muestran cómo la administración de múltiples vacunas pueden conducir a la inmunosupresión. Por otra parte, dos estudios en pacientes muestran que el factor GM-CSF estimulante de colonias de macrófagos y granulocitos, utilizado como adyuvante en vacunas, puede conducir a resultados adversos en términos de recaída y supervivencia. La modulación de la actividad de las células T reguladoras puede ser necesaria para superar este resultado y pueden ser cruciales para el desarrollo de vacunas terapéuticas.

En este artículo proponen el mecanismo por el cual las vacunas pueden causar inmunosupresión:



23. [Heffernan JM, Keeling MJ. 2009. Implications of vaccination and waning immunity. Proc. R. Soc. B. 276: 2071-2080]

For infectious diseases where immunization can offer lifelong protection, a variety of simple models can be used to explain the utility of vaccination as a control method. However, for many diseases, immunity wanes over time and is subsequently enhanced (boosted) by asymptomatic encounters with the infection. The study of this type of epidemiological process requires a model formulation that can capture both the within-host dynamics of the pathogen and immune system as well as the associated population-level transmission dynamics. Here, we parametrize such a model for measles and show how vaccination can have a range of unexpected consequences as it reduces the natural boosting of immunity as well as reducing the number of naive susceptibles. In particular, we show that moderate waning times (40–80 years) and high levels of vaccination (greater than 70%) can induce large-scale oscillations with substantial numbers of symptomatic cases being generated at the peak. In addition, we predict that, after a long disease-free period, the introduction of infection will lead to far larger epidemics than that predicted by standard models. These results have clear implications for the long-term success of any vaccination campaign and highlight the need for a sound understanding of the immunological mechanisms of immunity and vaccination.

- Para muchas enfermedades, la inmunidad desvanece con el tiempo y se ve reforzada posteriormente por encuentros asintomáticos con la infección.
- Utilizamos el modelo del sarampión para mostrar como la vacunación puede tener una serie de consecuencias inesperadas, ya que reduce el refuerzo natural de la inmunidad. Mostramos, en específico, que el tiempo de decadencia esperado es de unos 40-80 años y que los altos niveles de vacunación que se registran hoy en día (más de un 70%) puede inducir oscilaciones a gran escala, generando muchos casos asintomáticos.
- Además podemos predecir que, después de un periodo libre de enfermedad, a largo plazo, la introducción de la infección dará lugar a epidemias mucho más grandes que la predicha por los modelos estándar.

24. [Santos LS, Sant'anna LO, Ramos JN, Ladeira EM, Stavracakis-Peixoto R, Borges LLG, Santos CS, Napoleão F, Camello TCF, Pereira GA, Hirata R, Vieira VV, Cosme LMSS, Sabbadini PS, Mattos-Guaraldi AL. 2015. Diphtheria outbreak in Maranhão, Brazil: microbiological, clinical and epidemiological aspects. Epidemiol Infect. 143: 791-798]

We describe microbiological, clinical and epidemiological aspects of a diphtheria outbreak that occurred in Maranhão, Brazil. The majority of the 27 confirmed cases occurred in partially ($n=16$) or completely ($n=10$) immunized children ($n=26$). Clinical signs and characteristic symptoms of diphtheria such as cervical lymphadenopathy and pseudomembrane formation were absent in 48% and 7% of the cases, respectively. Complications such as paralysis of lower limbs were observed. Three cases resulted in death, two of them in completely immunized children. Microbiological analysis identified the isolates as *Corynebacterium diphtheriae* biovar intermedius with a predominant PFGE type. Most of them were toxigenic and some showed a decrease in penicillin G susceptibility. In conclusion, diphtheria remains endemic in Brazil. Health professionals need to be aware of the possibility of atypical cases of *C. diphtheriae* infection, including pharyngitis without pseudomembrane formation.

- Se describen los aspectos microbiológicos, clínicos y epidemiológicos de un brote de difteria en Maranhão, Brasil. La mayoría de los casos confirmados ocurrió en niños parcialmente o completamente inmunizados. Signos clínicos característicos de la difteria como la formación de seudomembrana y linfadenopatía cervical eran ausentes en el 48% y 7% de los casos, respectivamente. Se observaron complicaciones como parálisis de miembros inferiores. Tres casos resultaron en muerte, dos de ellos en niños completamente inmunizados.
- El análisis microbiológico identificó el *Corynebacterium diphtheriae* biovar intermedius con un tipo PFGE predominante. La mayoría de ellos eran toxígenos y algunos mostraron una disminuida susceptibilidad a la penicilina G.
- Conclusión: la difteria sigue siendo endémica en Brasil y los profesionales deben ser conscientes de la posibilidad de que surjan casos atípicos de infección por *C. diphtheriae*, incluyendo faringitis sin formación de seudomembrana.

25. [Pellegrino P, Carnovale C, Pozzi M, Antoniazzi S, Perrone V, Salvati D, Gentili M, Brusadelli T, Clementi E, Radice S. 2014. On the relationship between human papilloma virus vaccine and autoimmune diseases. *Autoimmunity Reviews*. 13: 736-741]

A B S T R A C T

The human papilloma virus (HPV) vaccines were introduced to reduce the incidence of cervical cancer. The bivalent vaccine is effective against HPV-16, -18, -31, -33 and -45 while the quadrivalent vaccine is effective against HPV-16, 18, 31, 6 and 11 types. The immunisation, recommended for adolescent females, has led to high vaccine coverage in many countries.

Along with the introduction of the HPV vaccines, several cases of onset or exacerbations of autoimmune diseases following the vaccine shot have been reported in the literature and pharmacovigilance databases, triggering concerns about its safety. This vaccination programme, however, has been introduced in a population that is at high risk for the onset of autoimmune diseases, making it difficult to assess the role of HPV vaccine in these cases and no conclusive studies have been reported thus far.

We have thus analysed and reviewed comprehensively all case reports and studies dealing with either the onset of an autoimmune disease in vaccinated subject or the safety in patients with autoimmune diseases to define the role of the HPV vaccines in these diseases and hence its safety. A solid evidence of causal relationship was provided in few cases in the examined studies, and the risk vs. benefit of vaccination is still to be solved. The on-going vigilance for the safety of this vaccine remains thus of paramount importance.

- La vacuna contra el papiloma humano se introdujo para reducir la incidencia de cáncer cervical.
- Junto con la introducción de las vacunas bivalentes y tetravalentes contra el VPH, varios casos de exacerbación de enfermedades autoinmunes aparecen, lo que provocó preocupaciones acerca de su seguridad. Sin embargo, este programa de vacunación se ha introducido en una población de alto riesgo para la aparición de enfermedades autoinmunes, por lo que es difícil evaluar el papel de la vacuna en estos casos. Así pues hemos analizado y revisado exhaustivamente todos los informes de casos y estudios relativos a cualquier aparición de una enfermedad autoinmune en el sujeto vacunado.
- En unos pocos casos se ha establecido una relación causal, y el balance riesgo-beneficio de la vacuna aun esta por resolver.
- La vigilancia en curso para la seguridad de esta vacuna sigue siendo por lo tanto de suma importancia.

Los autores de este artículo también añaden un cuadro de mensajes claves del estudio, en el cual se incluye el siguiente:

- La decisión de vacunar contra el VPH es una de carácter personal y no debe ser implementada en nombre de la salud pública. El VPH no es una enfermedad letal en 95% de las infecciones, y el otro 5% es detectable y tratable en la etapa precancerosa.

26. [Kanduc D. 2009. Quantifying the posible cross-reactivity risk of an HPV16 vaccine. *Journal of Experimental Therapeutics and Oncology*. 8: 65-76]

Background: The potential adverse events associated with vaccination for infectious diseases underscore the need for effective analysis and definition of possible vaccine side effects. Using the HPV16 proteome as a model, we quantified the actual and theoretical risks of anti-HPV16 vaccination, and defined the potential disease spectrum derived from concomitant cross-reactions with the human organism.

Methods: We searched the primary sequence of the HPV16 proteome for heptamer aminoacid sequences shared with human proteins using the Protein International Resource database.

Results: The human proteome contains 82 heptapeptides and two octapeptides found in HPV16. The viral matches are spread among proteins involved in fundamental processes, such as cell differentiation and growth and neurosensory regulation. The human proteins containing the HPV16-derived heptamers include cell-adhesion molecules, leukocyte differentiation antigens, enzymes, proteins associated with spermatogenesis, transcription factors, and neuronal antigens. The number of viral matches and their locations make the occurrence of side autoimmune cross-reactions in the human host following HPV16-based vaccination almost unavoidable.

Conclusions: Any antigen-based vaccine needs to be carefully and thoroughly designed and critically screened for potential side effects by comparing sequence similarity at the molecular level.

Antecedentes: Los posibles efectos adversos asociados con la vacunación contra enfermedades infecciosas, subrayan la necesidad de analizar y definir el riesgo de las vacunas. Nosotros utilizamos como modelo el proteoma HPV16 y cuantificamos sus riesgos reales y teóricos de la vacunación contra HPV16. También definimos el espectro de enfermedades cruzadas concomitantes que se pueden dar en el organismo como resultado de la vacunación.

Métodos: Buscamos la secuencia primaria del proteoma HPV16 y buscamos secuencias heptaméricas compartidas con proteínas humanas utilizando el Protein International Resource Database.

Resultados: El proteoma humano contiene 82 heptapéptidos y dos octapéptidos encontrados en HPV16 también. Estas secuencias compartidas con el proteoma humano son proteínas involucradas en la diferenciación celular, el crecimiento, y la regulación neurosensorial. Específicamente, encontramos secuencias heptaméricas compartidas con la vacuna en proteínas humanas como: moléculas de adhesión, antígenos de diferenciación de leucocitos, enzimas, proteínas asociadas con la espermatogénesis, factores de transcripción y antígenos neuronales.

-Estas secuencias compartidas hacen que la aparición de reacciones cruzadas autoinmunes después de la vacunación a base de HPV16 sea casi inevitable.

Conclusiones: Cualquier vacuna basada en antígeno necesita ser diseñada minuciosamente y tiene que evaluarse sus posibles efectos secundarios basada en la secuencia del antígeno y su comparación a nivel molecular con proteínas humanas.

27. [Chang J, Campagnolo D, Vollmer TL, Bompreszi R. 2011. Demyelinating disease and polyvalent human papilloma virus vaccination. *J Neurol Neurosurg Psychiatry*. 82(11): 1296-1298]

Since its inception, the polyvalent vaccine against the human papilloma virus (HPV), Gardasil, has generated some controversies as a temporal relationship between the administrations of the vaccine and the development of a few autoimmune diseases, such as acute disseminated encephalomyelitis (ADEM), multiple sclerosis (MS) and Guillain-Barre syndrome have been reported.¹⁻³ We encountered two cases whose initial presentation of CNS demyelination followed in close time relationship the administration of Gardasil vaccine and we discuss their possible association.

-La vacuna polivalente contra el VPH, Gardasil, ha generado mucha controversia desde su creación, ya que se han reportado relaciones entre su administración y la subsecuente aparición de enfermedades autoinmunes, tales como encefalomiелitis diseminada aguda, esclerosis múltiple y síndrome de Guillain Barre.

-Nos encontramos con dos casos con presentación inicial de desmielinización del SNC seguidos en estrecha relación temporal a la administración de Gardasil. Discutimos su posible asociación.

Los autores concluyen que es muy probable que en estos casos haya individuos genéticamente predispuestos a montar una respuesta inmunitaria exagerada a la administración de una vacuna. Esto puede culminar, pues, en una autoinmunidad.

-Creen que es importante recoger más casos para poder documentar los efectos adversos de la vacuna y determinar su seguridad y eficacia.

28. [Sutton I, Lahoria R, Tan IL, Clouston P, Barnett MH. 2009. CNS demyelination and quadrivalent HPV vaccination. *Multiple Sclerosis*. 15: 116-119]

Vaccination is generally considered safe in patients with multiple sclerosis (MS). We report five patients who presented with multifocal or atypical demyelinating syndromes within 21 days of immunization with the quadrivalent human papilloma virus (HPV) vaccine, Gardasil®. Although the target population for vaccination, young females, has an inherently high risk for MS, the temporal association with demyelinating events in these cases may be explained by the potent immuno-stimulatory properties of HPV virus-like particles which comprise the vaccine. A prospective case-control study of patients with MS or clinically isolated demyelinating syndromes receiving the Gardasil® vaccine may provide relevant safety data in this population. *Multiple Sclerosis* 2009; 15: 116-119. <http://msj.sagepub.com>

-La vacunación se considera segura generalmente en pacientes con esclerosis múltiple. Presentamos cinco pacientes con síndromes desmielinizantes multifocales o atípicos, generados 21 días después de la inmunización con la vacuna tetravalente del VPH.

-Aunque la población objetivo, mujeres jóvenes, es una población de alto riesgo inherente para la esclerosis múltiple, la asociación temporal con eventos desmielinizantes en estos cinco casos pueden explicarse por las potentes propiedades inmuno-estimuladoras de la vacuna

29. [Tomljenovic L, Shaw CA. 2012. Death after Quadrivalent Human Papillomavirus (HPV) Vaccination: Causal or Coincidental? Pharmaceut Reg Affairs. S12:001]

Abstract

Background: The proper understanding of a true risk from vaccines is crucial for avoiding unnecessary adverse reactions (ADRs). However, to this date no solid tests or criteria have been established to determine whether adverse events are causally linked to vaccinations.

Objectives: This research was carried out to determine whether or not some serious autoimmune and neurological ADRs following HPV vaccination are causal or merely coincidental and to validate a biomarker-based immunohistochemical (IHC) protocol for assessing causality in case of vaccination-suspected serious adverse neurological outcomes.

Methods: Post-mortem brain tissue specimens from two young women who suffered from cerebral vasculitis-type symptoms following vaccination with the HPV vaccine Gardasil were analysed by IHC for various immuno-inflammatory markers. Brain sections were also stained for antibodies recognizing HPV-16L1 and HPV-18L1 antigen which are present in Gardasil.

Results: In both cases, the autopsy revealed no anatomical, microbiological nor toxicological findings that might have explained the death of the individuals. In contrast, our IHC analysis showed evidence of an autoimmune vasculitis potentially triggered by the cross-reactive HPV-16L1 antibodies binding to the wall of cerebral blood vessels in all examined brain samples. We also detected the presence of HPV-16L1 particles within the cerebral vasculature with some HPV-16L1 particles adhering to the blood vessel walls. HPV-18L1 antibodies did not bind to cerebral blood vessels nor any other neural tissues. IHC also showed increased T-cell signalling and marked activation of the classical antibody-dependent complement pathway in cerebral vascular tissues from both cases. This pattern of complement activation in the absence of an active brain infection indicates an abnormal triggering of the immune response in which the immune attack is directed towards self-tissue.

Conclusions: Our study suggests that HPV vaccines containing HPV-16L1 antigens pose an inherent risk for triggering potentially fatal autoimmune vasculopathies.

Practice implications: Cerebral vasculitis is a serious disease which typically results in fatal outcomes when undiagnosed and left untreated. The fact that many of the symptoms reported to vaccine safety surveillance databases following HPV vaccination are indicative of cerebral vasculitis, but are unrecognized as such (i.e., intense persistent migraines, syncope, seizures, tremors and tingling, myalgia, locomotor abnormalities, psychotic symptoms and cognitive deficits), is a serious concern in light of the present findings. It thus appears that in some cases vaccination may be the triggering factor of fatal autoimmune/neurological events. Physicians should be aware of this association.

-Es necesario entender el verdadero riesgo que conllevan las vacunas para prevenir efectos adversos innecesarios. Aun y así, a fecha de hoy, no hay evidencias sólidas o criterios establecidos para determinar cuáles de los efectos adversos tienen como causa las vacunas.

- Queremos determinar si algunas de las enfermedades autoinmunes y neurológicas que aparecen después de la vacuna contra el VPH tienen una relación coincidente o causal. Utilizamos evidencia inmunohistoquímica para evaluar la posible relación.

-Muestras *post-mortem* de tejido cerebral de dos mujeres jóvenes que padecieron síntomas relacionados con vasculitis cerebral, posterior a la administración de la vacuna *Gardasil*, fueron examinadas con varios marcadores inmunoinflamatorios. También marcamos muestras con anticuerpos contra los antígenos HPV-16L1 y HPV-18L1, presentes en *Gardasil*.

-En ambos casos, la autopsia no reveló ningún resultado anatómico, microbiológico o toxicológico que pudiese explicar la muerte de estas mujeres.

-No obstante, nuestro análisis inmunohistoquímico mostró evidencia de una vasculitis autoinmune, potencialmente desencadenada por una reacción cruzada de los anticuerpos contra HPV-16L1 uniéndose a la pared de los vasos sanguíneos cerebrales en todas las muestras. También detectamos la presencia de partículas de HPV-16L1 dentro de la vasculatura cerebral, algunas de ellas adheridas a la pared vascular.

-Los anticuerpos contra HPV-18L1 no se adhirieron a los vasos cerebrales o cualquier otro tejido neuronal.

-La inmunohistoquímica también reveló un incremento en la señalización de las células T y una activación marcada en la cascada clásica del complemento en tejidos vasculares cerebrales en ambos casos.

-Este patrón de activación del complemento, en ausencia de una infección cerebral activa, indica un funcionamiento alterado del sistema inmunitario de tipo autoinmune.

-Nuestro estudio sugiere que las vacunas contra el VPH que contienen antígenos HPV-16L1, suponen un riesgo para la aparición de vasculopatías autoinmunes.

- Implicaciones prácticas: Muchos síntomas reportados sobre la seguridad de la vacuna en las bases de datos son indicadoras de vasculitis cerebral, pero no se reconocen como tal: migrañas intensas y persistentes, síncope, convulsiones, temblores... De aquí surge una grave preocupación, considerando nuestros resultados. El personal sanitario debe ser consciente de esta asociación.