Communication of vaccine benefit
beyond the infection prevented

Les Pensières Center for Global Health
Veyrier-du-Lac - France

4-6 December 2017

The "Fluad Case" in Italy: could it have been dealt differently?

Paolo Bonanni

Department of Health Sciences (DSS)

University of Florence, Italy

Conflicts of interest disclosure

Paolo Bonanni received grants for epidemiological and HTA research from different vaccine companies (GSK, SPMSD, Novartis, Pfizer, MSD, Seqirus) and fees for taking part to advisory boards on different vaccines from the same companies

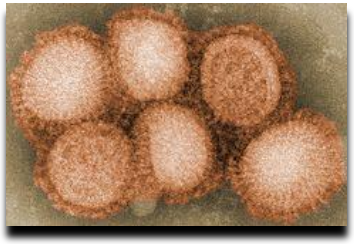
FLUAD®

- Egg-derived, surface-antigen, trivalent inactivated inter-pandemic influenza vaccine, adjuvanted with MF59
- Indicated for use in persons ≥65 y
- Approved in Europe in **1997**
- **MF59C.1**, a squalene based oil-in-water emulsion

  (9.75 mg squalene, 1.175 mg of polysorbate 80, 1.175 mg of sorbitan trioleate, 0.66 mg of sodium citrate dihydrate and 0.04 mg of citric acid monohydrate)
- Seroprotection: within 2 to 3 weeks
- Duration of post-vaccination immunity: 6 -12 months

3 influenza strains recommended for influenza season 2014-2015

- A/California/7/2009 NYMC X-181 (H1N1)
- A/Texas/50/2012 NYMC X-223 (H3N2)
- B/Massachusetts/2/2012 – (wild type)



Adverse event information

AR from clinical trials

Common (>1/100, <1/10):

- **Systemic reactions**: fever, malaise, shivering, fatigue, headache, sweating, myalgia (muscular pain), arthralgia (joint pain).
- **Local reactions: redness**, swelling, **pain** at the injection site, ecchymosis (bruising), **induration**
- **These reactions usually disappear within 1-2 days without treatment.**

http://drug.fda.moph.go.th/zone_search/files/2C_20_45_N_FLUAD.pdf

AR from post-marketing surveillance

Uncommon (>1/1,000, <1/100):

- Generalised skin reactions (pruritus, urticaria or non-specific-rash.

Rare (>1/10,000, <1/1,000):

- Neuralgia, paraesthesia, convulsions, transient thrombocytopenia
- Allergic reactions, in rare cases leading to shock

Very rare (<1/10,000):

- Vasculitis with transient renal involvement and exudative erythema multiforme
- Neurological disorders: encephalomyelitis, neuritis and Guillain Barré syndrome
- Asthenia, Influenza-Like Illness (ILI), pain in the extremity, muscular weakness, lymphadenopathy.

Vaccination campaign 2014-2015: Fluad distribution

About **4 million** doses were distributed in **Italy**

3 elderly (87, 79 e 68 y) between 12 and 18 November

- On 27 November 2014 the use of batch **142701** and batch **143301** was **suspended** in Italy **as a precautionary measure** owing to 4 reported serious cases of AR observed in a short time after Fluad administration (**3 deaths within 48 hours from vaccination**)

- According to AIFA: "A full picture will be formed only after a full analysis of all aspects, including the **general health** of the patients, their **ages** and probable **conditions** they might have had"

http://www.agenziafarmaco.gov.it/it/content/aifa-dispone-il-divieto-di-utilizzo-due-lotti-del-vaccino-antinfluenzale-fluad

1st case in Sicily, man aged 68 years

28 NOV - Fabio Fichera, il medico di famiglia che ha vaccinato, ad Augusta in Sicilia, il paziente di 68 anni morto subito dopo il vaccino anti- influenza nel suo studio, vuole fare chiarezza e alcune precisazioni su quanto riferito dalla stampa in merito alla vicenda avvenuta il 12 novembre scorso. Il caso di cui ci ha riferito il dottor Fichera è uno dei quattro eventi avversi (di cui tre mortali) che hanno portato ieri l'Aifa alla decisione di vietare la vendita in via cautelativa di due lotti del vaccino Fluad della Novartis.

"Il mio paziente – dice a *Quotidiano Sanità* – è tornato nel mio studio dopo circa un'ora in cui si era recato al mercato. È entrato, aveva le mani al petto e lamentava un forte dolore. L'ho fatto subito sdraiare ma poco dopo ha perso conoscenza. A quel punto, io e i miei due colleghi dello studio, dopo aver fatto chiamare immediatamente il 118, abbiamo cominciato a praticargli il massaggio cardiaco e a seguire abbiamo messo in atto tutte le procedure necessarie in questi casi".

CARDIOVASCULAR EVENT 1 HOUR AFTER VACCINATION

"È stata un'esperienza drammatica. Umanamente dura", Fichera fa ancora fatica a parlare della vicenda ma aggiunge che quanto accaduto "per quanto ne sappiamo, ha solo un legame temporale con la somministrazione del vaccino. Non si può dire altro". L'autopsia – riferisce il medico, a Firenze per il congresso della Simg, la società' scientifica dei medici di famiglia – è stata eseguita e al momento si è in attesa dei risultati dei patologi.

Fichera prima di concludere vuole però ribadire l'importanza del vaccino e si augura che non si diffonda il panico, perché spiega "ci abbiamo messo anni per arrivare alla copertura vaccinale di oggi. Il rischio è che in poche settimane tutto vada in fumo. Bisogna tener conto che la vaccinazione è consigliata proprio alle persone più fragili. E sono migliaia quelle che si vaccinano. È ovvio che con questi numeri, ci possano essere dei decessi che sono solo temporalmente legati alla profilassi, tenendo conto che si vaccinano soprattutto persone più a rischio. Bisogna ricordare a tutti che il vero pericolo per le persone con alcune patologie è l'influenza".

28 November 2014 www.quotidianosanità.it

Other 2 deaths

un siciliano di 87 anni e una molisana di 79, sono deceduti entro 48 ore dalla somministrazione, per un'infiammazione del sistema nervoso centrale, (un'encefalite-meningite).

MENINGITIS/ENCEPHALITIS

- **87 y.o. man**

- **79 y.o. woman in Molise**

28/11/2014 www.focus.it/scienza/salute/vaccini-anti-influenzali-e-morti-sospette-che-cosa-ce-da-sapere

27-30 November: hysteria brought on by media coverage of the deaths

VACCINI KILLER, MORTI SOSPETTE E LOTTI: TUTTI I NUMERI DI 4 GIORNI D'ALLARME

Leggo

Vaccino, le morti sospette ora sono 11. Aifa: «Non escluso ritiro altri lotti»

Il Messaggero 28/11/2014

«Due lotti incriminati del vaccino sono stati bloccati dall'AIFA già ieri. Si tratta in tutto di 500mila dosi, distribuite in 12 Regioni, ma solo nelle Asl e non in farmacia. L'allarme, però, potrebbe allargarsi perché l'Aifa non esclude il ritiro di altri lotti del vaccino poiché fra le 8 nuove segnalazioni di morti giunte oggi, alcune riguardavano persone che avevano utilizzato il vaccino di altri lotti»

Tens of thousands of vaccines had been injected around the country. In Tuscany, 60,000 doses of the two recalled lots of Fluad had been administered before the recall was issued

FIRENZE - 29/11

- Il vaccino sospetto iniettato anche nel Grossetano
- La testimonianza: "Mia madre stava per iniettarselo"

Il Tirreno 28/11/2014

Segnalato oggi in RNF nuovo decesso con FLUAD

Aggiornamento AIFA

13 deaths

30/11/2014

L'AIFA ha ricevuto in data odierna tramite la Rete Nazionale di ***Farmacovigilanza*** la segnalazione di un nuovo caso di decesso avvenuto in concomitanza temporale con la somministrazione del vaccino antinfluenzale FLUAD, prodotto da Novartis Vaccines and Diagnostics. Si tratta di una paziente di 83 anni affetta da gravi patologie e in politerapia. Complessivamente il numero di decessi presenti nella Rete Nazionale sale a 13. Le segnalazioni riguardano 8 Regioni: Sicilia (2); Molise (1); Puglia (2); Toscana (2); Emilia Romagna (2); Lombardia (2); Lazio (1) e Umbria (1).

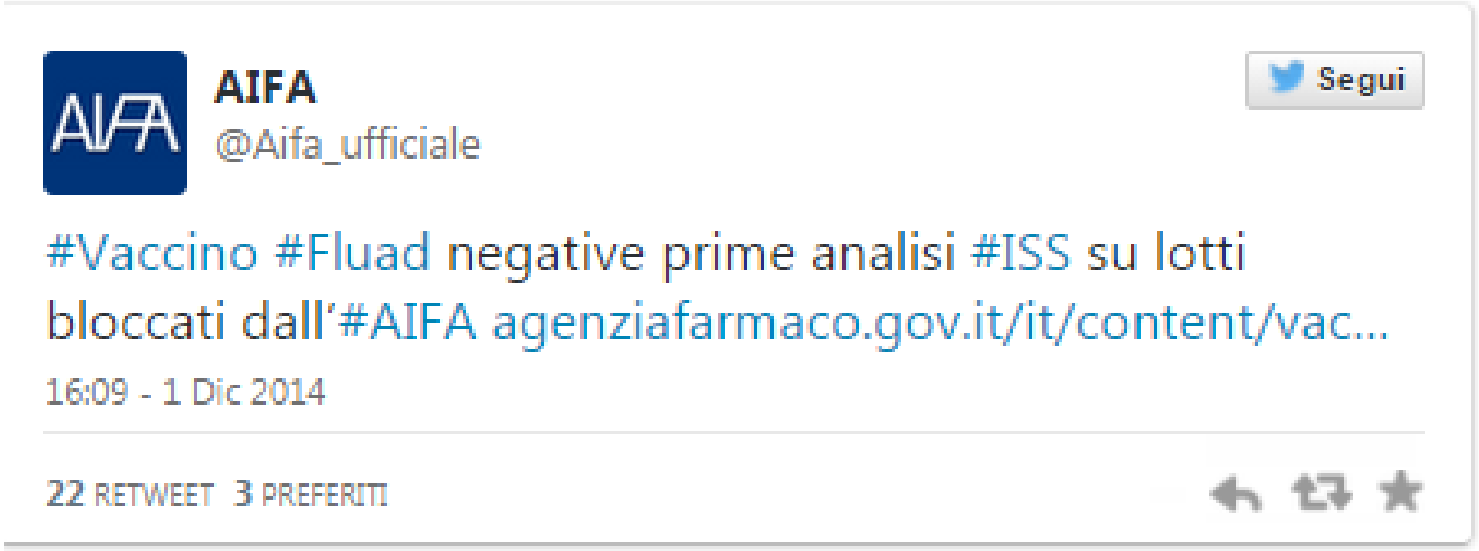
Domani avrà inizio l'esame approfondito dell'intera problematica in sede europea presso il Comitato per la Valutazione dei Rischi e la ***Farmacovigilanza*** dell'Agenzia Europea dei Medicinali, che si concluderà entro giovedì 4 dicembre.

Immediate consequences

- AIFA "We are getting other reports that we are examining," and other lots of the vaccine may be withdrawn; “the new reports may be linked to a possible contamination”
- “Deaths that had been linked to the vaccine were mainly cardiovascular-related and could have been the result of pre-existing illnesses”
- Novartis defended its "robust" safety record
- Regional health authorities across Italy weighed whether to temporarily suspend flu vaccinations
- Health authorities in Liguria and in Veneto regions, but also in Rome, suspended flu vaccinations while clinics and pharmacies checked their stocks for the suspicious batches
- Codacons, one of the most important and representative consumers association in Italy, asked the MoH to suspend the vaccination campaign

30/11/2014 www.ansa.it

1/12/2014: Italian Institute of Health (ISS) announced the first tests results



In preliminary tests:

- No evidence of contamination
- No defects in production
- No endotoxins
- Content and characteristics of the vaccine virus antigen: compliant with quality standards
- The characteristics of the reported deaths already seem to rule out contamination by microorganisms

- The Italian Rapporteur presented information on the reported serious AEs for advice by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) on the review performed

4/12/2014

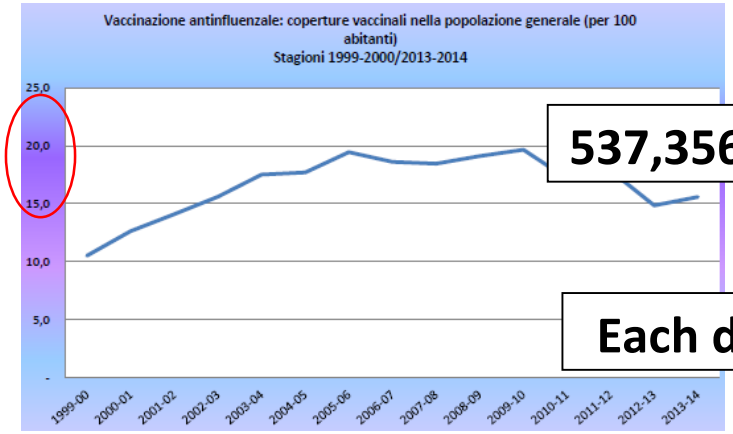
- The PRAC took into account
  - the likely **high population exposure to the vaccine over the previous 2 months**
  - the **background mortality rate in the general population ≥65 y.o.**
  - **the lack of a consistent clinical pattern** amongst the serious AEs leading to a fatal outcome
- considered that the reports were unrelated to vaccination
- **concluded that** there was **no evidence of a causal link between Fluad and the AEs reported**

23/12/2014

- ISS released the **final test results** (**abnormal toxicity test** and **sterility test**) confirming the vaccine safety
- the ban on the Fluad batches was removed

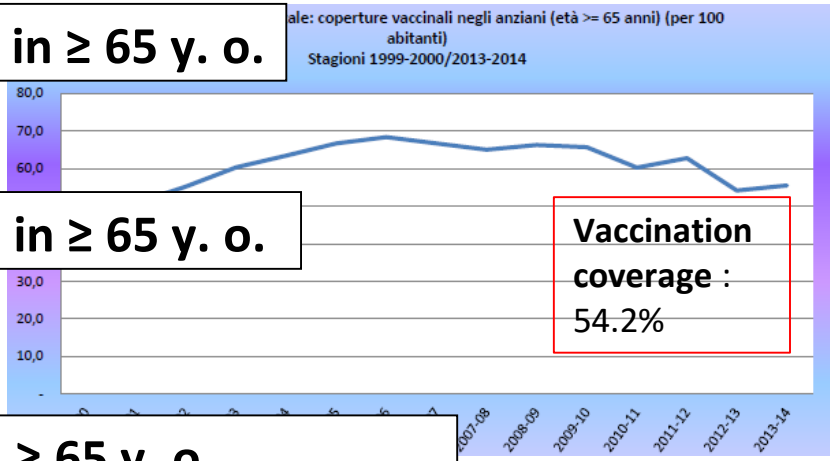
ISTAT 2012

613,520 total deaths



537,356 (87.6%) deaths in ≥ 65 y. o.

Each day 1,472 deaths in ≥ 65 y. o.



Vaccination coverage : 54.2%

Each day 798 deaths in ≥ 65 y. o. who have been vaccinated against influenza disease

Each day 38 deaths in ≥ 65 y. o. within 48 h from vaccine administration

15-20 if we consider a lower vaccination coverage (i.e. 50%) and subtracting subjects with contraindications

http://dati.istat.it/Index.aspx?DataSetCode=DCIS_CMORTE1_EV&Lang=#

Knowledge of the background incidence of events which may occur in temporal relationship with a vaccine

- Essential for assessing a cluster of events in terms of the strength of the signal

- In **Israel**, during the early phases of the annual influenza immunization campaign in **October 2006**, **4 deaths** occurred among **elderly** vaccinees and **the campaign was temporarily halted for an investigation**. It was determined that the **expected death rate among similarly aged vaccinees within seven days** of a vaccine exposure was 0.01 to 0.02% and this rate had been **constant for several years prior to the apparent signal**. **The background rate for death in the population was relatively high as a result of age and comorbid conditions.**

- The importance of understanding background rates of disease prior to a mass campaign were pointed out **in a study** published in October 2009.

Black et al. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines. *Lancet*, 2009, 374:2115;2122.

«*Media reporting bias*» according to the AIFA Chairman of the Board

«The increase in the number of serious AEs reported is the result of the impact of the media coverage of the event on both HCW and private citizens»

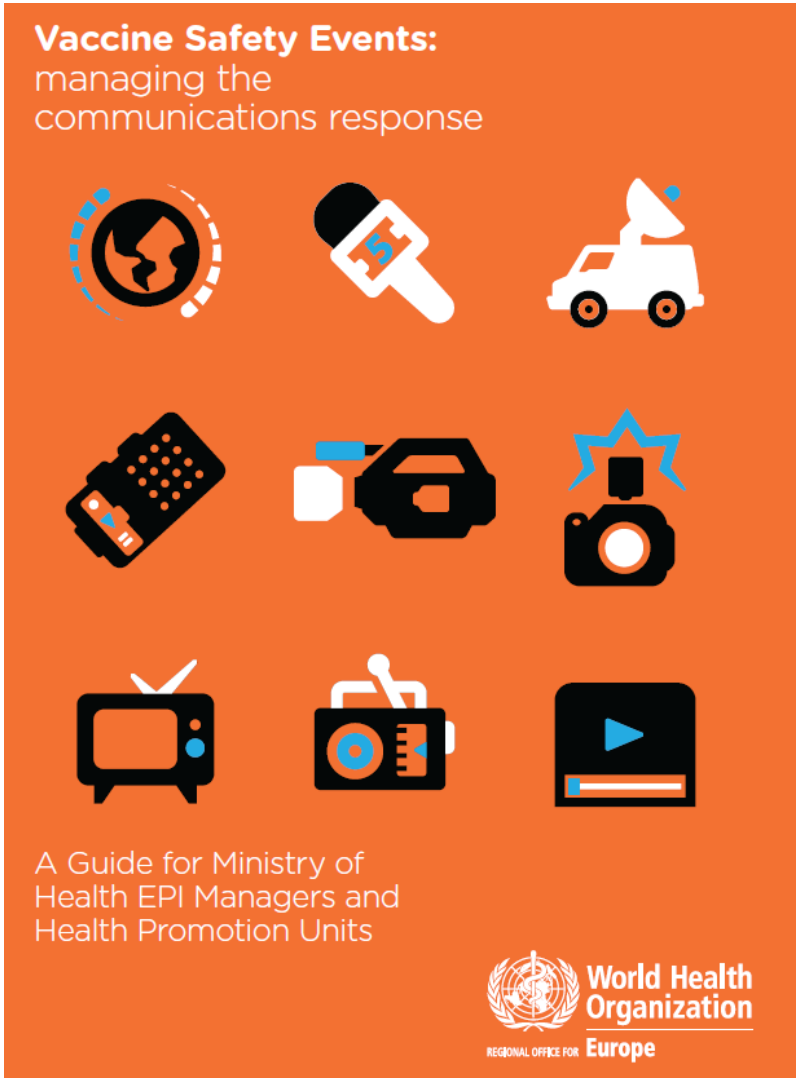
e&p anno 39 (4) luglio-agosto 2015

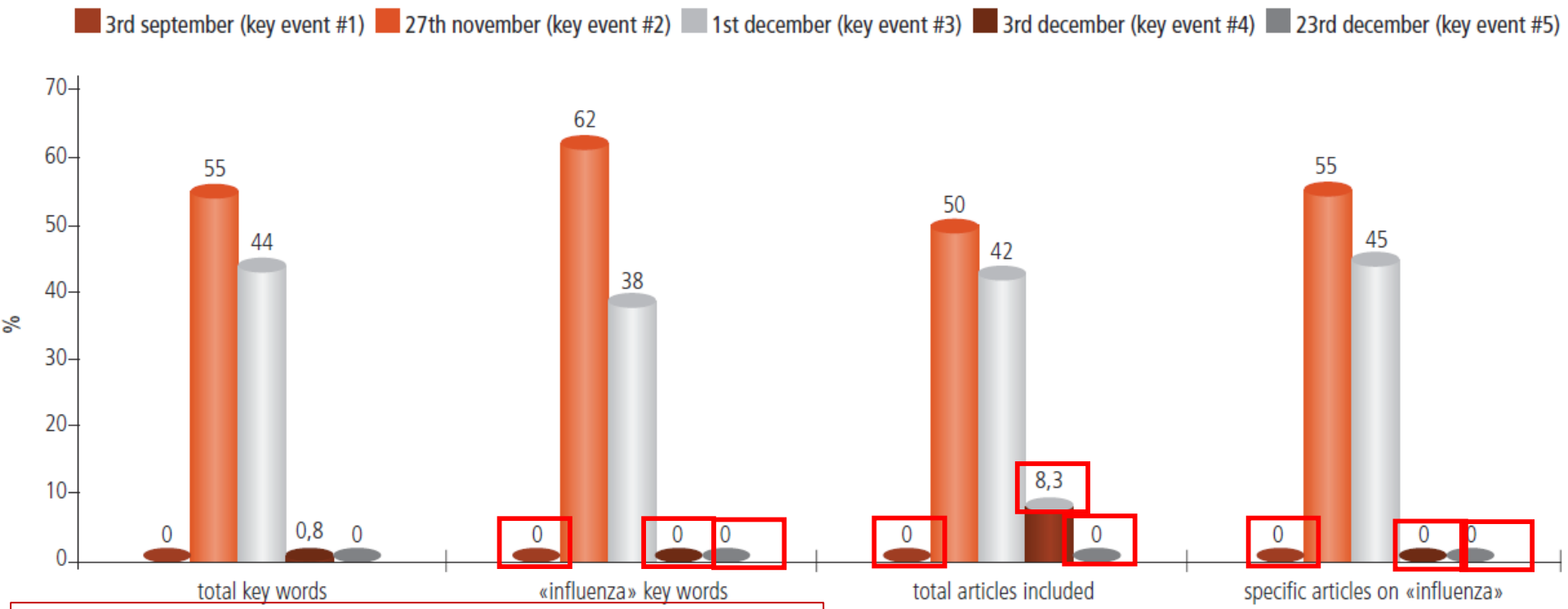
Influenza and immunization: a quantitative study of media coverage in the season of the «Fluad case»

Informazione: risultati di un'indagine di monitoraggio nella stagione del «caso Fluad»

Anna Odone, Valentina Chiesa, Veronica Ciorba, Paola Cella, Cesira Pasquarella, Carlo Signorelli

The ease with which information can be disseminated now means that negative comments about vaccines can go "viral" on the internet without balanced professional input





Key event #1: 3rd Sept. - Release of the MoH' Circular containing recommendations for influenza prevention

Key event #2: 27th Nov.- Reporting of 3 deaths surmised to be associated with Fluad and suspension of 2 batches

Key event #3: 1st Dec. - First safety results released

Key event #4: 3rd Dec. – PRAC conclusions released

Key event #5: 23rd Dec. – Final safety results released

- No articles focusing on influenza and influenza immunization were published on key date #1.
- 2 articles were published around the start of the immunization campaign. They were placed on page 31 and 53 of the newspaper: one was a 23-word long article placed at the bottom of the page, the other focused on influenza without mentioning the approaching influenza immunization campaign

Negative events are far more noticeable than positive ones

Odone A, Chiesa V, Ciorba V, Cella P, Pasquarella C, Signorelli C. Influenza and immunization: a quantitative study of media coverage in the season of the «Fluad case». **Epidemiol Prev**. 2015 Jul-Aug;39(4 Suppl 1):139-45.

Attempts by scientific societies to counter the panic

Cricelli (Simg): "Ogni giorno muoiono 800 anziani che si sono vaccinati per l'influenza, senza che vi sia alcuna correlazione con il vaccino"

Anche la Società Italiana di Medicina Generale ribadisce l'importanza della vaccinazione antinfluenzale

29/11/2014

"Ogni giorno, secondo le statistiche, muoiono 800 anziani che si sono vaccinati per l'influenza, ma non c'è alcuna correlazione tra il vaccino e i decessi". Lo ha affermato oggi Claudio Cricelli, presidente della Società Italiana di Medicina Generale (Simg). "I dati dell'Istat dicono che ogni giorno in Italia muoiono circa 1800 persone, con punte fino a duemila nei mesi invernali - ha sottolineato Cricelli - La maggior parte dei decessi, circa 1600 al giorno, avviene in persone anziane. Il tasso vaccinale supera il 50% negli over 65. Quindi ogni giorno muoiono circa 800 persone che si sono vaccinate. Non vi è alcuna correlazione tra la somministrazione del vaccino e i decessi. Salvo circostanze eccezionali, tutte da dimostrare, le cause della morte sono le solite: cancro, malattie cardiovascolari, respiratorie e altro". Secondo Cricelli il legame tra vaccini e morti sospette è smentito dai dati epidemiologici. "Dobbiamo dunque ricondurre gli eventi che si stanno verificando nelle ultime ore a una seria analisi scientifica. - ha sottolineato - Come dimostrano i dati epidemiologici a nostra disposizione, è evidente che le morti fra gli anziani, da sempre, sono più frequenti e non sono causate dalla vaccinazione antinfluenzale. Gli anziani - ha aggiunto Cricelli - costituiscono la popolazione più fragile e, indipendentemente dalla vaccinazione antinfluenzale, fanno registrare percentuali di mortalità più elevate. Ma, proprio per la loro condizione di fragilità, è importante che si vaccinino contro l' influenza. Altrimenti assisteremmo a un numero di morti sicuramente maggiore".

The 2014-2015 seasonal influenza immunization coverage per Region

Vaccinazione antinfluenzale: stagione 2014-2015. Coperture vaccinali per 100 abitanti

Regione	CLASSI DI ETA'								
	6-23m	2-4 a	5-8 a	9-14 a	15-17 a	18-44 a	45-64 a	≥65	Totale
Piemonte	0,2	0,3	0,6	0,7	0,8	1,3	5,7	46,3	13,5
Valle d'Aosta	0,2	0,3	0,3	0,6	0,6	1,3	5,6	43,5	11,9
Lombardia	0,4	0,7	0,8	0,6	0,5	0,9	3,3	46,3	11,4
P. A. Bolzano	0,1	0,5	0,6	0,4	0,5	0,8	3,7	36,6	8,3
P. A. Trento	1,6	1,3	1,4	1,3	0,9	1,2	5,3	51,9	12,9
Veneto	0,8	1,4	1,3	1,2	1,2	2,0	7,1	53,4	14,5
Friuli Venezia Giulia	0,1	0,1	0,1	0,8	0,8	1,6	7,1	49,0	15,0
Liguria	0,4	1,1	1,2	0,9	0,6	2,1	5,2	46,6	15,3
Emilia Romagna	0,7	1,2	1,4	1,5	1,4	2,0	8,1	50,0	14,9
Toscana	4,3	6,6	5,3	3,1	1,9	2,3	9,3	49,9	16,3
Umbria	0,1	0,2	0,3	0,4	0,5	1,4	7,4	61,8	17,8
Marche	0,3	0,7	0,9	0,8	1,1	1,5	6,9	46,2	13,5
Lazio	0,4	0,9	1,1	1,2	1,4	2,5	9,4	49,5	14,0
Abruzzo	0,2	0,5	0,5	0,6	1,1	1,6	6,4	38,5	11,1
Molise	0,1	0,6	0,7	0,8	1,1	2,3	11,6	49,0	15,7
Campania	1,7	3,2	3,5	2,4	3,1	2,8	11,4	52,9	13,9
Puglia	4,1	6,7	6,2	4,2	3,0	2,5	10,8	48,6	14,6
Basilicata	1,0	1,6	1,6	1,4	1,7	2,5	8,8	45,6	13,5
Calabria	0,9	1,2	1,6	1,2	2,5	1,6	6,6	53,3	13,4
Sicilia	0,1	0,4	0,6	0,6	1,2	2,4	8,7	47,4	12,8
Sardegna	1,1	2,8	3,3	2,2	1,7	2,0	7,4	40,6	12,0
Totale	**1,1**	**1,8**	**1,9**	**1,5**	**1,5**	**1,9**	**7,5**	**48,6**	**13,6**

Aggiornamento 18 settembre 2015

Source: Ministry of Health- ISS, available at:
http://www.salute.gov.it/imgs/C_17_tavole_19_allegati_iitemAllegati_0_fileAllegati_itemFile_2_file.pdf

Seasonal influenza immunization coverage -COMPARISONS 1999-2015

General Population

Elderly people (aged ≥65 years)

Vaccinazione antinfluenzale: coperture vaccinali negli anziani (età >= 65 anni) (per 100 abitanti)

Stagioni 1999-2000/2014-2015

Regione	1999-00	2000-01	2001-02	2002-03	2003-04	2004-05	2005-06	2006-07	2007-08	2008-09	2009-10	2010-11	2011-12	2012-13	2013-14	2014-15
Piemonte	33,8	44,7	48,3	51,5	55,7	55,9	58,8	59,3	58,9	60,7	60,6	57,3	55,0	51,6	51,1	46,3
Valle d'Aosta	35,8	56,6	54,5	56,0	55,3	54,4	63,1	54,2	61,0	54,5	58,9	55,6	56,2	47,0	48,2	43,5
Lombardia	39,6	46,7	53,8	58,7	60,9	65,3	64,0	63,1	58,6	61,7	63,1	54,2	57,9	48,2	48,6	46,3
P.A. Bolzano	n.p.	43,3	38,8	46,8	51,1	52,0	55,2	48,0	50,5	50,8	47,7	44,5	42,5	35,8	33,9	36,6
P. A. Trento	42,4	48,3	50,5	54,6	57,8	60,0	67,6	69,2	64,6	68,0	67,0	61,8	62,2	56,3	55,8	51,9
Veneto	47,3	60,7	63,5	n.p.	70,9	n.p.	73,2	74,1	70,3	71,6	71,2	67,8	67,1	58,9	58,5	53,4
Friuli Venezia Giulia	63,5	70,0	71,1	72,2	72,4	72,5	72,1	0,0	64,4	68,1	49,7	62,4	61,8	55,2	56,1	49,0
Liguria	37,7	42,3	54,2	59,6	62,5	66,1	65,3	67,5	65,6	65,7	65,7	58,0	55,6	41,6	50,4	46,6
Emilia Romagna	46,2	58,4	61,9	66,5	70,3	73,0	75,1	76,1	73,6	73,7	73,8	63,4	64,7	56,3	57,2	50,0
Toscana	36,0	51,9	51,7	56,7	61,5	62,2	67,6	70,3	68,5	69,5	71,1	68,8	67,8	58,9	60,2	49,9
Umbria	45,5	51,7	58,1	59,3	62,2	61,9	65,9	69,0	70,5	74,7	77,5	75,2	74,0	67,9	68,8	61,8
Marche	53,5	60,8	62,9	65,3	67,1	68,0	68,0	67,1	65,4	66,9	66,5	63,9	62,2	54,9	57,5	46,2
Lazio	26,7	46,5	60,5	67,5	69,5	71,5	73,3	74,1	68,0	67,9	67,7	64,1	62,2	56,8	56,8	49,5
Abruzzo	42,5	50,2	53,7	64,0	67,9	70,0	69,9	78,1	72,8	68,4	67,1	60,9	59,7	50,3	54,6	38,5
Molise	46,7	61,4	61,4	66,9	73,7	72,3	71,4	72,6	73,3	72,3	73,7	65,6	60,5	49,4	59,5	49,0
Campania	38,1	62,3	n.p.	75,6	72,3	71,9	72,9	73,2	68,2	72,2	63,4	58,2	73,1	61,4	61,3	52,9
Puglia	38,0	49,0	62,9	64,8	68,4	70,5	75,4	71,5	68,7	73,8	73,0	71,7	69,0	57,2	61,0	48,6
Basilicata	45,6	42,3	46,7	61,8	69,9	66,4	64,5	71,2	70,7	72,2	72,6	63,6	63,1	58,6	58,0	45,6
Calabria	23,6	29,7	n.p.	43,9	55,1	59,9	66,3	68,4	65,6	69,8	63,0	55,8	65,6	49,8	56,5	53,3
Sicilia	41,4	47,8	47,4	61,2	63,8	69,7	67,5	56,4	n.p.	61,0	64,1	61,3	60,2	54,0	56,5	47,4
Sardegna	30,0	39,4	46,9	52,4	43,9	59,2	56,1	49,3	39,8	49,6	60,9	59,6	57,0	47,3	46,0	40,6
Italia	**40,7**	**50,7**	**55,2**	**60,3**	**63,4**	**66,6**	**68,3**	**66,6**	**64,9**	**66,2**	**65,6**	**60,2**	**62,7**	**54,2**	**55,4**	**48,6**

http://www.salute.gov.it/portale/temi/p2_6.jsp?lingua=italiano&id=679&area=influenza&menu=vaccinazione

FLU VACCINATION DEATHS

Deaths after Fluad flu vaccine and the epidemic of panic in Italy

Carlo Signorelli *president*, Anna Odone *member*, Michele Conversano *member*, Paolo Bonanni *member*

Italian Society of Hygiene, Preventive Medicine and Public Health (SItI), 00144 Rome, Italy

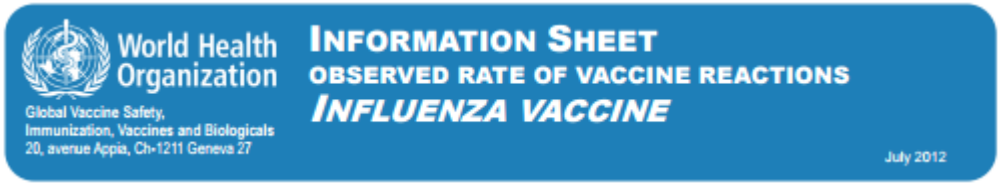
"Is it time to rethink pharmacovigilance regulations on vaccines to prevent outbreaks of generalized panic from compromising immunisation campaigns and negatively affecting disease related outcomes, thereby generating extremely serious health and economic losses for individuals and society?"

BMJ 2015 (Published 14 January 2015)

Causality assessment

- is the **systematic review of data** about an AEFI case
- it aims to determine the **likelihood** of a causal association
- Identifying a coincidental AEFI that is falsely attributed to a vaccine product is vital
- It is **seldom possible to achieve a straightforward answer to the question** "Did the vaccine given to a particular individual cause the particular event reported?"
- In most cases the assessment involves **systematic consideration of all possible causes of an AEFI** in order to arrive at a conclusion

- **WHO information sheets on rates of vaccine reactions are available online** http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/
- http://www.who.int/vaccine_safety/initiative/tools/Influenza_Vaccine_rates_information_sheet.pdf?ua=1



- **Temporal relationship**: The **vaccine exposure must precede** the event
- **Definitive proof that the vaccine caused the event**: **Clinical or laboratory proof**
- **Population-based evidence for causality** – i.e. what is known about "Can it?"
- **Biological plausibility**: In situations where there is no clear "yes" or "no" answer, biological plausibility may provide support for or against vaccine causality
- **Consideration of alternative explanations**: **it is important to consider "coincidental AEFI".** All reasonable alternative etiological explanations should be considered, including:
  - **preexisting / newly acquired illness**
  - **spontaneous occurrence of an event without known risk factors**
  - **other exposures to drugs or toxins prior to the event**
  - **surgical or other trauma that leads to a complication**
  - **a manifestation of, or complication of, a coincidental infection that was present before or was incubating at the time of immunization**
- **Prior evidence that the vaccine in question could cause a similar event**

Evidence for other causes

Association with the vaccine product(s), immunization error or immunization anxiety (within an appropriate time window)

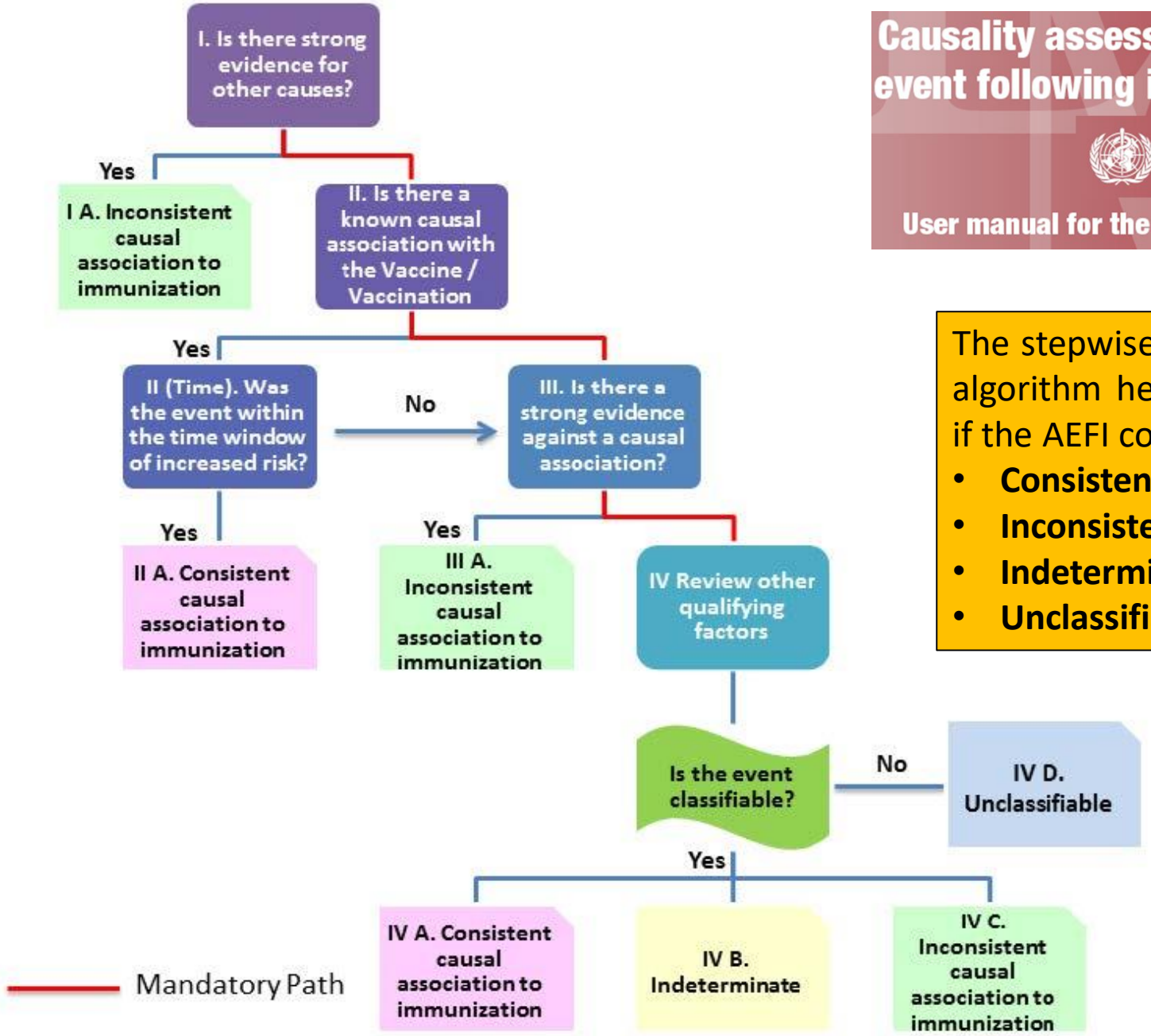
Causality Assessment Checklist

Evidence against a causal association

Other qualifying factors for classification such as the **background rate of the event, present and past health conditions, potential risk factors, medication, biological plausibility etc.**

I. Is there strong evidence for other causes?	Y N UK NA	Remarks
Does a clinical examination, or laboratory tests on the patient, confirm another cause?	☐☐☐☐	
II. Is there a known causal association with the vaccine or vaccination?		
Vaccine product(s)		
Is there evidence in the literature that this vaccine(s) may cause the reported event even if administered correctly?	☐☐☐☐	
Did a specific test demonstrate the causal role of the vaccine or any of the ingredients?	☐☐☐☐	
Immunization error		
Was there an error in prescribing or non-adherance to recommendations for use of the vaccine (e.g. use beyond the expiry date, wrong recipient etc.)?	☐☐☐☐	
Was the vaccine (or any of its ingredients) administered unsterile?	☐☐☐☐	
Was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal at the time of administration?	☐☐☐☐	
Was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	☐☐☐☐	
Was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?	☐☐☐☐	
Was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?	☐☐☐☐	
Immunization anxiety		
Could the event have been caused by anxiety about the immunization (e.g. vasovagal, hyperventilation or stress-related disorder)?	☐☐☐☐	
II (time). If "yes" to any question in II, was the event within the time window of increased risk?		
Did the event occur within an appropriate time window after vaccine administration?	☐☐☐☐	
III. Is there strong evidence against a causal association?		
Is there strong evidence against a causal association?	☐☐☐☐	
IV. Other qualifying factors for classification		
Could the event occur independently of vaccination (background rate)?	☐☐☐☐	
Could the event be a manifestation of another health condition?	☐☐☐☐	
Did a comparable event occur after a previous dose of a similar vaccine?	☐☐☐☐	
Was there exposure to a potential risk factor or toxin prior to the event?	☐☐☐☐	
Was there acute illness prior to the event?	☐☐☐☐	
Did the event occur in the past independently of vaccination?	☐☐☐☐	
Was the patient taking any medication prior to vaccination?	☐☐☐☐	
Is there a biological plausibility that the vaccine could cause the event?	☐☐☐☐	

CAUSALITY ASSESSMENT ALGORITHM



Causality assessment of an adverse event following immunization (AEFI)

World Health Organization

User manual for the revised WHO classification

The stepwise approach of the algorithm helps to determine if the AEFI could be:

- **Consistent**
- **Inconsistent**
- **Indeterminate outcome**
- **Unclassifiable**

EU pharmacovigilance system

- All medicinal products in the EU are subject to a strict testing and assessment of their quality, efficacy and safety before being authorised
- Once placed on the market they continue to be monitored so to assure that any aspect which could impact the safety profile of a medicine is detected and assessed and that necessary measures are taken (**pharmacovigilance)**
- Regulation (EC) No 726/2004 → centrally authorised medicinal products
- Directive 2001/83/EC → nationally authorised medicinal products
- The EU **pharmacovigilance legislation has been subject to a major review** that led to the adoption of new legislation in 2010 (APPLICABLE IN **JULY 2012**)
    - REGULATION (EU) No 1235/**2010**
    - DIRECTIVE **2010**/84/EU
    - REGULATION (EU) **2012**/1027/EU
    - DIRECTIVE **2012**/26/EU (WHICH STARTED TO APPLY **FROM JUNE AND OCTOBER 2013**)
- The EMA has released **good pharmacovigilance practice guidelines** (GVP) in order to **facilitate the performance of pharmacovigilance activities**.

Main pillars of the new legislation

- **Strengthening** and **rationalising** the system
- It improves patient safety and public health through **better prevention**, **detection** and **assessment** of ADRs
- **New definition for ADR: "**Noxious and unintended effects resulting
  - from the **authorised use** of a medicinal product at normal doses
  - also from **medication errors**
  - uses **outside the terms of the marketing authorisation**, including the **misuse** and **abuse** of the medicinal product"

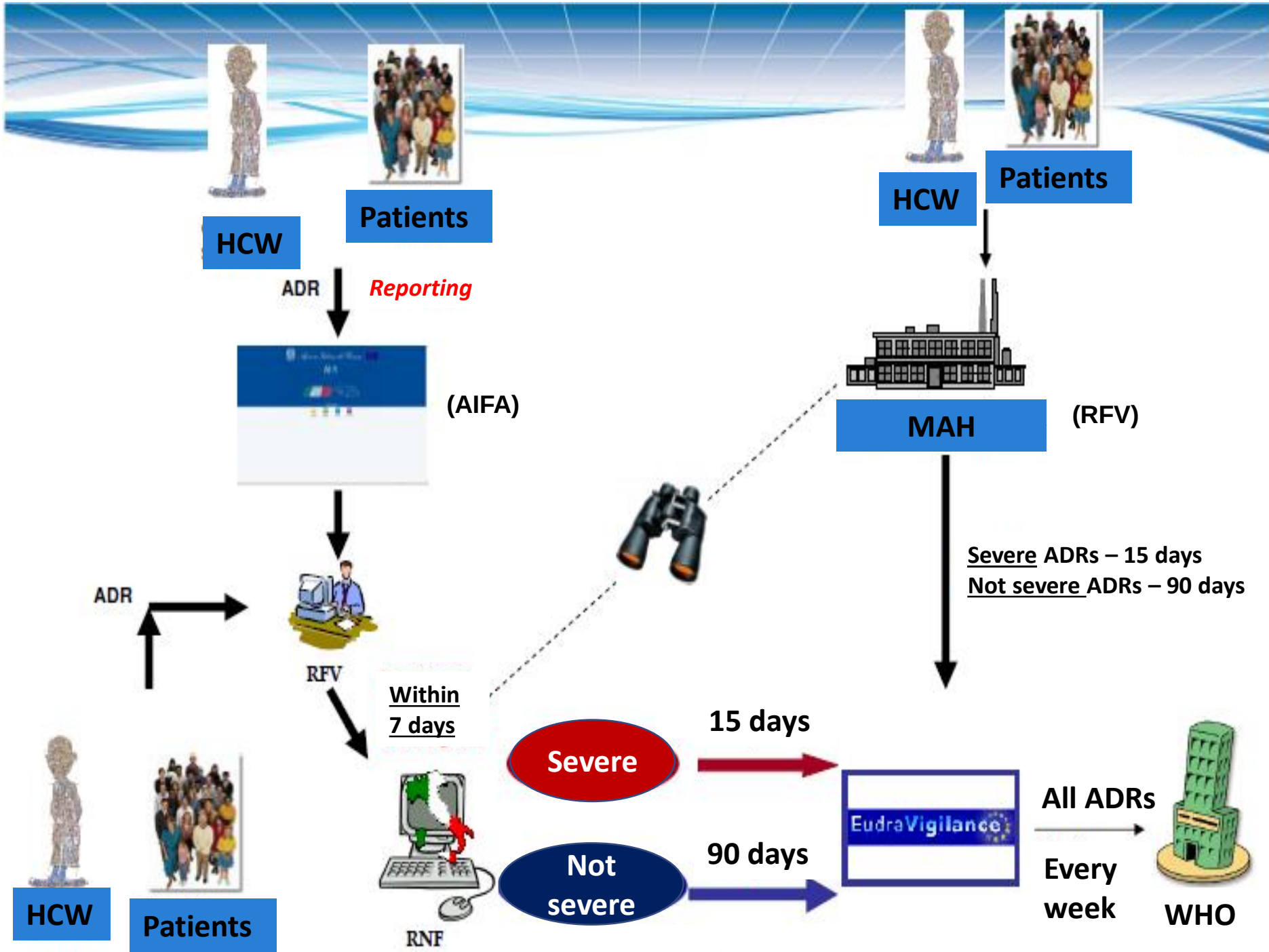
- **It also allows patients to report ADRs directly to the competent authorities**
- **Clear tasks and responsibilities for all parties** (marketing authorisation holders (MAH), competent authorities, EMA)
- Establishment of a **new scientific committee** at the EMA: the **Pharmacovigilance Risk Assessment Committee** (PRAC)

http://ec.europa.eu/health/human-use/pharmacovigilance/index_en.htm

The Italian National Network of Pharmacovigilance (RNF)

- Pharmacovigilance: regulated in Italy by the provisions contained in Title IX of Italian Legislative Decree 219/2006 and the provisions contained in **Italian Legislative Decree 42/2014**, which **Ministerial Decree 30/4/2015** implement in Italy Directive 2012/26/EU of the European Parliament and of the Council
- Spontaneous ADRs are collected through **the National Network of Pharmacovigilance** throughout the national territory that includes:
  - Regional Authorities and the Autonomous Provinces of Trento and Bolzano
  - the Regional Centres of Pharmacovigilance
  - >200 Local Health Authorities
  - 100 Hospitals
  - 43 Research Institutes
  - >800 Pharmaceutical Companies
  - AIFA
- The RNF is also operating in connection with the European network for pharmacovigilance EudraVigilance that collects in a single database all data provided at national level by the EU countries

http://ec.europa.eu/health/human-use/pharmacovigilance/index_en.htm


HCW
Patients
ADR
Reporting
(AIFA)
HCW
Patients
MAH
(RFV)
Severe ADRs – 15 days
Not severe ADRs – 90 days
ADR
RFV
Within
7 days
Severe
15 days
Not
severe
90 days
EudraVigilance
All ADRs
Every
week
WHO
HCW
Patients
RNF

Difficult assessment of causality between AEs and vaccines in mass vaccination programmes

- Signal detection should be **as real-time as possible**, ideally to inform decision-making as the vaccination progresses
- With **high vaccine uptake**, **incident cases of many natural diseases** in given population cohorts **will occur in temporal association with vaccination**

Priorities:

- to **rapidly identify possible new signals**
- **to rapidly assess the likelihood that the number of reports may be consistent with the expected background incidence in the vaccinated cohort**
- **Effective communication** about safety is **difficult**
- New **suspected ARs must be very rapidly investigated and distinguished from coincidental illnesses**

Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases

SIGNAL DETECTION

SINGLE REPORT OF A SERIOUS AE

- **A single report of a serious AE occurring in temporal association with the vaccination, especially if the event is unexpected or fatal,** could have a **detrimental** impact on vaccination programmes due to perception of unsubstantiated risks or risk amplification
- A single report of a serious adverse event **should be processed as a signal only if there is a possible causal association to the vaccine**
- **This requires adequate information** on:
  - **clinical course of the event**
  - **medical history**
  - **vaccination history**
  - **co-medication**
  - details of the vaccine(s) administered (brandname, batch number, route of administration and dose)
- **Signal validation** should also be based on **contextual information**
- If adequate data are available on the number of vaccinated individuals of the same age category**, the observed and expected numbers of cases should be estimated**

Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases

BATCH-SPECIFIC SIGNAL ACTION IN THE ABSENCE OF A KNOWN QUALITY ISSUE

- **In the absence of a known quality issue, decision making on a precautionary recall or quarantine is difficult, as a causal association with the vaccine can rarely be established at the time when an initial decision is required.**
- **For single fatal adverse events, particularly where the cause of death is unknown, the reporting rate of the event *relative to both the usage of the vaccine batch* and *the 'expected' age-specific all-cause mortality* should be considered before deciding on a recall or quarantine action**
- **The probability of a chance association should be considered.** If a fatal event is initially thought to be a consequence of a known adverse reaction (e.g. due to anaphylaxis), it would not necessarily imply a batch-specific issue requiring a recall or a quarantine.
- **On the other hand, where contamination of a batch is suspected** based on individual case details or a localised cluster, due to possible cold chain and handling deviations, **localised action should be considered before escalation to a national recall or quarantine.**

Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases

SAFETY COMMUNICATION

- **Appropriate communication** is essential
- Communication **should help preventing anxiety-related reactions**
- **Any potential risks should be clearly communicated**
- Safety communication about a vaccine should also describe the **benefits of vaccines**
- **Communication planning should include being prepared for frequent public communication needs**, such as those regarding **excipients**, **residues**, identified or potential risks for individuals with special conditions, **coincidental events**, **temporal versus causal association**
- **Relevant background rates**, by age group and sex, **of signs and symptoms should be kept up-to-date, as well as exposure data**
- Communication planning should also include **preparing standard texts**. **Concerns raised by the public should also be addressed by proactively communicating results of benefit-risk evaluations.**
- **Competent authorities** should ensure **appropriate communication** with the public and **in particular the media**

Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases

Steps to implementing the media communications plan	
Pre-crisis	• Establish a crisis communications team. • Prepare a list of those in and outside the organization who should be informed when a crisis occurs. • Prepare a list of key spokespersons. • Inform all employees as to who are the designated spokespersons. • Ensure potential spokespersons are media trained. • Identify and assign all tasks for responding to a crisis. • Assemble information about your media; identify current links, potential new links that can be developed and their audiences, etc. • Distribute the communication plan to relevant people.
During crisis	• Adapt the plan to ensure it achieves a well-defined objective in this crisis. • Select the spokesperson. • Develop background information as well as drafting press releases. • Define audience(s) (there may be several e.g. public, professionals). • Define key messages for each audience and for each scenario. • Identify delivery mechanisms for each major audience (e.g. radio, newspaper, television, etc.).
Post crisis	• Evaluate your impact. • Revise your communications plan accordingly.

WHO Regional Office for Europe. Vaccine Safety Events: managing the communications response. A Guide for Ministry of Health EPI Managers and Health Promotion Units. Copenhagen, DK. 2013

CONCLUSIONS

- In our opinion, during the so-called ‘Fluad Case’, critical phases were those of signal detection, validation and exchange of information
- Withdrawal of batches is foreseen even in case of a single severe suspected AR, however other aspects should have been taken into consideration (biological plausibility, alternative causes)
- Reported deaths are within the number of expected deaths among vaccincated elderly population
- The media coverage had an impact in increasing vaccine hesitancy
- A task force for the management of vaccine crisis is strongly needed
- Better communication on vaccine safety to restore trust into this formidable primary prevention tool is of crucial importance

Regarding pretended hidden risks of vaccines

THANK YOU FOR YOUR ATTENTION!