Strategie di FV vaccini:

messaggi chiave

Nicola Magrini, DG AIFA

Presentazione Rapporto Annuale Sicurezza Vaccini Covid19

Roma, 9 Febbraio 2022

Nel linguaggio della moderna teoria dell'informazione, si può dire che l'informazione è *una differenza che produce una differenza* …

e che le differenze sono rapporti

Gregory Bateson,

Ultima conferenza, 1979

FV: 3 livelli

- FV spontanea (ADR) – voluntary reporting – signal detection
  - Identification of unknown or incompletely documented drug-event association
  - Limitations: challenges with determination of causality and the lack of a comparison group to assess excess vs baseline risk in a given population.
- Osservato – atteso: signal refinement
  - Rapid substantiation of signals using evidence from different sources / simplified pharmaepi studies
  - Rapid cycle analysis (RCA): observed number of adverse events is compared with the expected number of events,with the expected number of events determined from prior data, a concurrent comparison control group, or self-control methods. Weekly VSD comparisons assess many safety outcomes of interest; as such, the threshold for statistical significance is adjusted to account for multiple outcomes and multiple data assessments.
- Studi analitici da large DB – signal validation
  - Signal validation - Risk quantification and characterization
  - Studi analitici: case-referent studies and self-controlled methods

La conoscenza della safety è a 4 livelli

1. **RCT: Sicurezza come emerge da valutazione B/R**
2. FV spontanea (ADR) – voluntary reporting – signal detection
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   - Signal validation - Risk quantification and characterization
   - Studi analitici: case-referent studies and self-controlled methods

La conoscenza della safety è a 4 livelli

1. **RCT: Sicurezza come emerge da B/R**
    a. **I dati dei grandi studi registrativi – 94-95% di efficacia**
    b. **La efficacia reale (RWE) dei programmi di vaccinazione: simile alla efficacia dei trials ed graduale riduzione effetto (waning) a partire dal 3-4 mese per rischio reinfezione**

Covid-19 mRNA Vaccines — Six of One, Half a Dozen of the Other

Eric J. Rubin, M.D., Ph.D., and Dan L. Longo, M.D.

In many countries, the availability of vaccines has marked a turning point in the Covid-19 pandemic. Although the vaccines are imperfect, breakthrough infections in fully vaccinated people remain quite rare, even with recently emerging variants. Countries with high vaccination rates have largely been able to reopen, and rates of severe illness and death have dropped dramatically. But this has not been a smooth process. Different vaccines have become available at different times, and access to them has varied markedly from country to country. Thus, the

N ENGL J MED 386;2 NEJM.ORG JANUARY 13, 2022

Differenze tra i 2 RNA vaccines 1/2

- Although when we look at hundreds of thousands of recipients, mRNA-1273 is marginally more effective than BNT162b2, the death rate among vaccinated persons remains tiny, and the difference in the risk of death between the two vaccines was only approximately 0.2 per 10,000 vaccinees during the period marked by alpha-variant predominance.
- How the two vaccines compare with regard to side effects is difficult to assess without a head-to-head trial.

- We have two vaccines that vary slightly in effectiveness, although they are both highly effective. For any given person, the difference in vaccine efficacy between BNT162b2 and mRNA-1273 is unmeasurable

Rubin EJ and Longo DL.
Covid19 mRNA vaccines- six of one, half a dozen of the other
NEJM 2022, Jan 13

Differenze tra i 2 RNA vaccines 2/2

- In their analysis of documented SARSCoV- 2 infection over this 24-week period, they found that BNT162b2 was associated with 5.75 events per 1000 persons (95% confidence interval [CI], 5.39 to 6.23), whereas mRNA-1273 was associated with 4.52 events per 1000 persons (95% CI, 4.17 to 4.84) — a between-group difference of 1.23 events.

- Differences between the groups persisted for symptomatic infection (difference, 0.44 events per 1000), hospitalization (0.55 per 1000), ICU admission (0.10 per 1000), and death (0.02 per 1000).

- The between-group difference with respect to documented infection persisted and in fact grew during the 12-week period dominated by the delta variant (to 6.54 events per 1000 persons).

La conoscenza della safety è a 4 livelli

1. **RCT: Sicurezza come emerge da B/R**
    a. I dati dei grandi studi registrativi – 94-95% di efficacia
    b. La efficacia reale (RWE) dei programmi di vaccinazione: simile alla efficacia dei trials ed graduale riduzione effetto (waning) a partire dal 3-4 mese per rischio reinfezione
    c. **Effetto placebo/nocebo**

JAMA Network Open

Original Investigation | Public Health

Frequency of Adverse Events in the Placebo Arms of COVID-19 Vaccine Trials
A Systematic Review and Meta-analysis

Julia W. Haas, PhD; Friederike L. Bender, MS; Sarah Ballou, PhD; John M. Kelley, PhD; Marcel Wilhelm, PhD; Franklin G. Miller, PhD; Winfried Rief, PhD; Ted J. Kaptchuk

Abstract

IMPORTANCE Adverse events (AEs) after placebo treatment are common in randomized clinical drug trials. Systematic evidence regarding these nocebo responses in vaccine trials is important for COVID-19 vaccination worldwide especially because concern about AEs is reported to be a reason for vaccination hesitancy.

OBJECTIVE To compare the frequencies of AEs reported in the placebo groups of COVID-19 vaccine trials with those reported in the vaccine groups.

DATA SOURCES For this systematic review and meta-analysis, the Medline (PubMed) and Cochrane

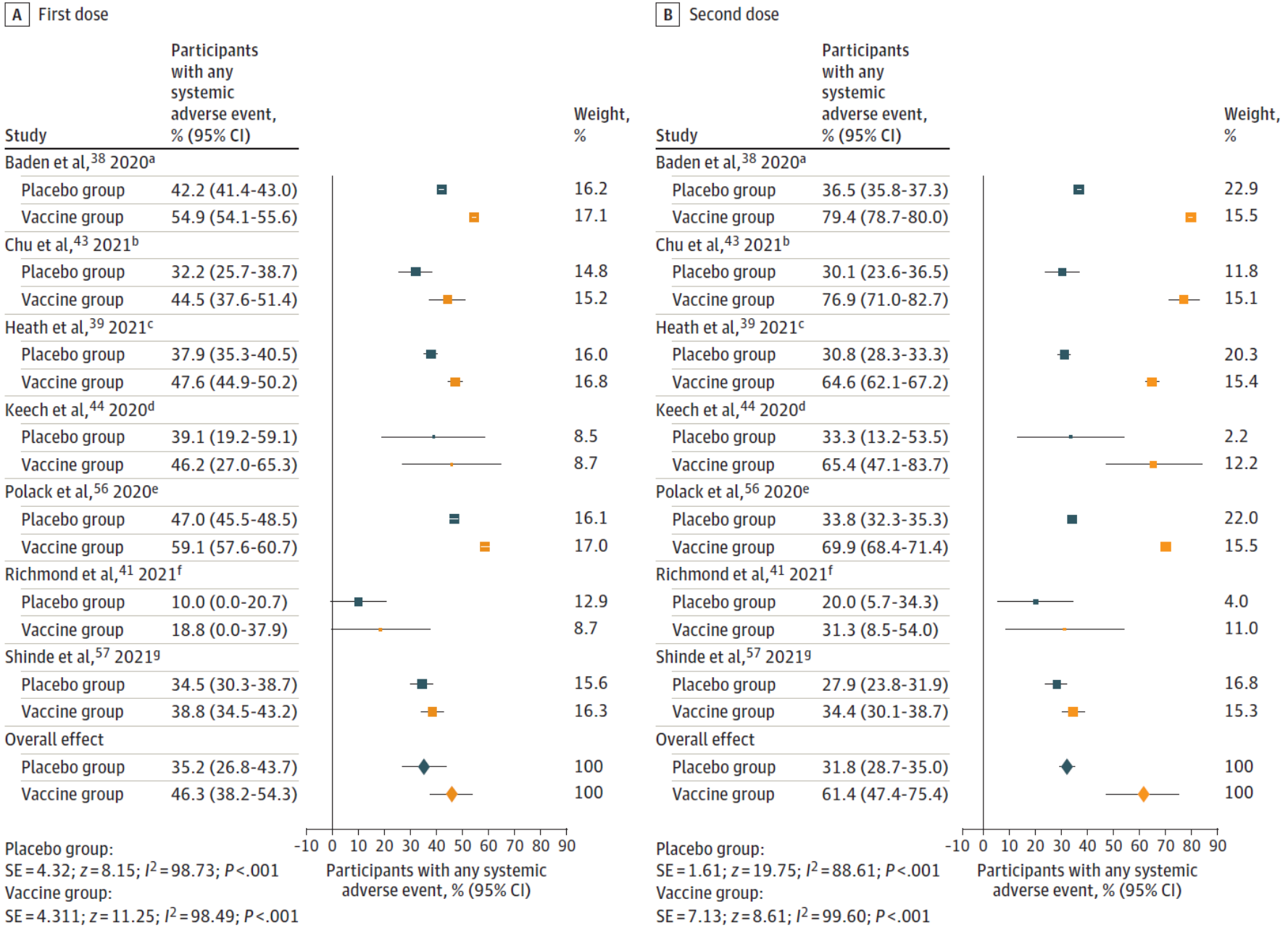
Findings In this systematic review and meta-analysis of 12 articles including AE reports for 45 380 trial participants, systemic AEs were experienced by 35% of placebo recipients after the first dose and 32% after the second. Significantly more AEs were reported in the vaccine groups, but AEs in placebo arms ("nocebo responses") accounted for 76% of systemic AEs after the first COVID-19 vaccine dose and 52% after the second dose.

Meaning This study found that the rate of nocebo responses in placebo arms of COVID-19 vaccine trials was substantial; this finding should be considered in public vaccination programs.

Placebo nocebo effect

Adverse events seemingly elicited by placebos are often called *nocebo responses*[14] and are thought to be caused by misattribution of routine background symptoms,[15] anxiety,[16] and expectations of AEs.[17,18] Emerging research has shown that informing patients about nocebo responses[19,20] and providing a positive framing of potential AEs[21-24] may be associated with reduced AE-related anxiety and nocebo responses. Although nocebo phenomena have been investigated in many contexts involving medication,[18,25-28] evidence of their influence in vaccination remains scarce. However, a recent meta-analysis suggested that a significant proportion of placebo recipients in influenza vaccine trials experienced systemic AEs, such as headache or fatigue, owing to nocebo responses.[29]

Figure 2. Forest Plots of Any Systemic Adverse Events After the First and Second Doses of the COVID-19 Vaccine or Placebo



Placebo nocebo effect

full disclosure and education about nocebo responses may be helpful.[19,20] For example, adding simple but accurate information about nocebo responses to the usual informed consent procedure (eg, "participants in the placebo arm of the randomized clinical trials testing this intervention reported similar AEs, probably because of worry and anxiety") helped reduce medication-related AEs in a clinical population.[20] Highlighting the probability of not experiencing AEs might also be beneficial.[21] Although more research on these communication strategies is needed, such honest information adds to full disclosure and is unlikely to cause harm. In addition, informing the public about the potential for nocebo responses may help reduce worries about COVID-19 vaccination, which might decrease vaccination hesitancy.[9,31]

> second dose, with headache and fatigue being the most common. This nocebo response accounted for 76.0% of systemic AEs after the first dose of COVID-19 vaccine, and for 51.8% after the second dose. Public vaccination programs should consider these high nocebo responses.

[…] uno spazio di discussione tra l'ambito regolatorio e quello più ampio ed articolato della comunità scientifica a degli operatori sanitari, delle associazioni dei malati e del mondo delle imprese, al fine di condividere aspetti metodologici, etici e di *governance* delle diverse tematiche che riguardano il mondo del farmaco.

Seminari Scientifici - AIFA

17 Feb 2021	**La resistenza antimicrobica: pensare l'impensabile** **>>> 1,508 iscritti**	**Mike Sharland** ***ST. GEORGE'S UNIVERSITY LONDON*** *WHO EML Antibiotic Working Group Chair*
15 Apr 2021	**Causalità e casualità nei recenti segnali di farmacovigilanza dei vaccini Covid-19: quali evidenze per le decisioni di salute pubblica?** **>>> 2,648 iscritti**	**Bernard Bégaud** **EMERITUS PROFESSOR OF CLINICAL PHARMACOLOGY, UNIVERSITY OF BORDEAUX** *Chair of the Scientific Committee EPI-PHARE*
19 Mag 2021	**Il sistema regolatorio oltre l'autorizzazione dei medicinali** **>>> 1,443 iscritti**	**Bert Leufkens** **UTRECHT UNIVERSITY** **Emeritus Professor of Regulatory Science**
24 Giu 2021	**Il consenso informato nelle sperimentazioni dei vaccini Covid-19:la soluzione è il problema?** **>>> 902 iscritti**	**Ezekiel J. Emanuel** **Levy University Professor** **Perelman School of Medicine and The Wharton Sch** **UNIVERSITY OF PENNSYLVANIA**

Messaggi chiave e conclusioni

A mo’ di

Offline: COVID-19 as culture war

Lancet, 22 Jan 2022

When Dr Anthony Fauci challenged Senator Rand Paul last week during US congressional hearings, he exposed how politicians have exploited the COVID-19 pandemic for their own personal advantage. Fauci showed screenshots of Senator Paul's website, which included the message "Fire Dr Fauci". He pointed out that Paul was inviting people to send donations to firefauci.org. He explained how Paul's exaggerations were creating

- Un eccesso di polarizzazione e strumentalizzazione politica del Covid19
- Una ridotta partecipazione dei medici e degli operatori sanitari alle discussioni sulle politiche sanitarie
- Una visione più chiara e coerente della nostra società nel post pandemia per un *build back fairer*, un ritorno a una normalità migliore

personal gain . As the pandemic enters its third year, the difficult truth is that the political debate about COVID-19 has evolved into a bitter culture war, where arguments have become struggles between different social groups holding different beliefs about how society should be constructed and governed. As one UK

error. On Dec 14, 2021, Dr Angelique Coetzee, a South African doctor with first-hand experience of managing patients infected with omicron, pointed out that the UK's reaction "is out of all proportion to the risks posed by this variant". Her message was clear: "I can reassure you that the symptoms presenting in those with Omicron are very, very mild compared with those we see with the far more dangerous Delta variant." Coetzee

version of the Paul–Fauci culture war. "It's Boris versus the scientists", proclaimed the front page of the *Daily Mail* on Dec 16, 2021. It took a month for the UK Health Security Agency to agree with the testimony of Coetzee that omicron caused a low severity of disease in adults.

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Vaccini Covid19, sicurezza e rapporto B/R

Una molteplicità di approcci ha confermato:

1. L'efficacia molto elevata dei vaccini Covid19 nel prevenire infezioni Covdi19 e soprattutto le forme gravi
2. Un rapporto beneficio rischi molto favorevole e una sicurezza complessiva molto elevata studiata in tutti gli ambiti (anche in ambiti salute riproduttiva, fertilità, …) con livelli di precisione delle stime mai visti prima
3. Una prevalenza di effetti indesiderati (fino al 75% degli effetti sistemici) riferibili al placebo (nocebo)
4. Una aperta e stretta collaborazione internazionale della *research community (della comunità dei ricercatori a livello internazionale)*
5. La possibilità di uscire dalla pandemia con l'dea di rafforzare i sistemi sanitari pubblici ed universalistici, la ricerca, la solidarietà sociale e l'equità globale

La filosofia consiste nell’imparare a vedere daccapo il mondo

Maurice Merleau-Ponty