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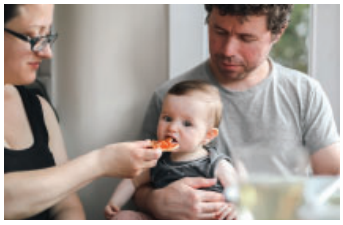
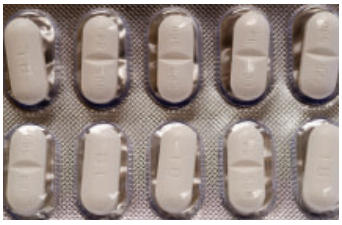


Maternal UPF intake and child excess weight p 59

Corroboration of potential drug safety signals p 60



Fluoroquinolones and risk of admission for suicidality p 62

ORIGINAL RESEARCH Results from three prospective cohort studies

Maternal consumption of ultra-processed foods and subsequent risk of offspring overweight or obesity

Wang Y, Wang K, Du M, et al

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Study question Is maternal ultra-processed food (UPF) intake while child rearing linked to risk of overweight or obesity in offspring during childhood and adolescence?

Methods This study used data from mothers and their children (19 958 mother-child pairs; 45% boys, aged 7-17 years at enrollment) who participated in the Nurses' Health Study II and Growing Up Today Study in the United States. Offspring were followed until the onset of overweight or obesity, loss to follow-up, or age 18. Multivariable adjusted log binomial models were used to estimate the relative risk of offspring overweight or obesity defined by the International Obesity Task Force.

Study answer and limitations 2471 (12.4%) offspring developed overweight or obesity. After adjusting for maternal risk factors and offspring's UPF intake, physical activity, and sedentary time, maternal intake of UPF while child rearing was associated with overweight or obesity in offspring, with a 26% higher risk in the highest intake group (group 5) versus lowest intake group (group 1; relative risk 1.26, 95% CI 1.08 to 1.47, P for trend<0.001). Some analyses were underpowered, particularly for peripregnancy intake.

What this study adds Maternal intake of UPF while child rearing was linked with an increased risk of overweight or obesity in offspring, independent of maternal and offspring lifestyle risk factors.

Funding, competing interests, and data sharing Supported by the National Institutes of Health, American Gastroenterological Association, the Crohn's and Colitis Foundation, American Cancer Society, and Massachusetts General Hospital. No competing interests. Study data available on request.

Maternal intake of ultra-processed foods (five equal groups) while child rearing and offspring overweight and obesity

Measure	Group 1	Group 2	Group 3	Group 4	Group 5	P for trend†
Overweight or obesity						
No (%)	458 (11.5)	438 (11.0)	501 (12.6)	480 (12.0)	594 (14.9)	—
Relative risk (95% CI)*	1 (reference)	1.00 (0.87 to 1.14)	1.11 (0.97 to 1.27)	1.07 (0.92 to 1.23)	1.26 (1.08 to 1.47)	<0.001
Obesity						
No (%)	164 (3.4)	181 (3.8)	171 (3.6)	210 (4.4)	272 (5.7)	—
Relative risk (95% CI)*	1 (reference)	1.1 (0.89 to 1.37)	1.02 (0.81 to 1.28)	1.14 (0.9 to 1.44)	1.35 (1.06 to 1.72)	<0.001

*Relative risk and 95% confidence interval (CI) estimated by generalized estimating equation. Models adjusted for maternal baseline age, race, total energy intake, 2010 Alternative Healthy Eating Index, body mass index, physical activity, smoking, history of chronic disease, living status, household income, and spouse's education, and for offspring's sex, ultra-processed food intake, physical activity, and sedentary time.
†Tested using standardized maternal ultra-processed food consumption as continuous variable.

Post-market oversight of medicine safety

ORIGINAL RESEARCH Cross sectional study

Characterization and corroboration of safety signals identified from the United States Food and Drug Administration Adverse Event Reporting System, 2008-19

Dhodapkar MM, Shi X, Ramachandran R, Chen EM, Wallach JD, Ross JS

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Study question How often do potential drug safety signals identified from the US Food and Drug Administration Adverse Event Reporting System (FAERS) result in regulatory action by the FDA, and are these actions corroborated by published research findings or public assessments by the Sentinel Initiative?

Methods A cross sectional study was conducted of potential safety signals identified from the FAERS publicly reported by the FDA between 2008 and 2019, and review of the relevant literature published before and after safety signals that were reported in 2014-15.

Study answer and limitations From 2008 to 2019, 603 potential safety signals identified from the FAERS were reported by the FDA, of which 413 (68.5%) were resolved (as of December 2021). Among the resolved potential safety signals, 91 (22.0%) led to no regulatory action and 322 (78.0%) resulted in regulatory action, including 319 (77.2%) changes in drug labeling and 59 (14.3%) drug safety communications or other public communications from the FDA. For a subset of 82 potential safety signals reported in 2014-15, a literature search identified 1712 relevant publications; 1201 (70.2%) were case reports or case series. Among these 82 safety signals, 76 (92.7%) were resolved. Relevant published research was identified for 57 (75.0%) of the resolved safety signals, 17 (29.8%) of which had at least one study that corroborated FDA regulatory action; relevant assessments by the Sentinel Initiative were identified for four (5.3%) signals, none of which corroborated FDA regulatory action. The corroboration analysis was limited to potential signals identified from the FAERS in 2014-15 to ensure most were resolved, and the quality of the published studies that corroborated regulatory action taken by the FDA was not considered.

What this study adds Most safety signals identified from the FAERS were resolved after several years, and 80% led to FDA regulatory action. Less than a third of regulatory actions were corroborated by published research findings or public assessments by the Sentinel Initiative, however, suggesting that either the FDA is taking regulatory actions based on evidence not made publicly available or that more comprehensive safety evaluations might be needed when potential safety signals are identified.

Funding, competing interests, and data sharing
No funding. Full details of competing interests on bmj.com. Data will be made available via a publicly accessible repository.

COMMENTARY Regulators should publish all evidence underlying their responses to safety signals

Harm from medicine use is an important public health concern, leading to many potentially preventable hospital admissions and deaths.[2-4] Early signals of serious harm, supported by evidence and acted on promptly, could lead to improved patient and public health.

In their study, Dhodapkar and colleagues analysed 12 years of safety signals identified within the US Food and Drug Administration's Adverse Event Reporting System (FAERS).[5] They asked how often these signals resulted in regulatory actions and whether they were corroborated by additional research. The 2007 FDA Amendments Act requires that the FDA publish quarterly reports of safety signals identified in FAERS.[6] This requirement is a welcome step, ensuring ongoing data mining for signals and rapid public access to information on potential harms.

Of 603 FAERS safety signals highlighted by the FDA from 2008 to 2019,[5] 190 (31.5%) remained unresolved by December 2021, and 91 (15%) others were judged not to require regulatory action. Actions to resolve the remaining 322 (53%) signals were mainly changes to product information. The FDA issued drug safety communications for 59 (9.8%) signals.

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Missing information

The rationale for differing regulatory actions after safety signals, or a lack of action, is often unclear. Some signals require substantial shifts in drug use; others might be false alarms; still others need more research to guide an informed response. The FDA routinely provides information on the evidence supporting drug safety communications. However, if the agency has only required a change to product information, usually no information is provided.[5] Dhodapkar and colleagues carried out a detailed analysis of 82 signals identified in 2014 and 2015;

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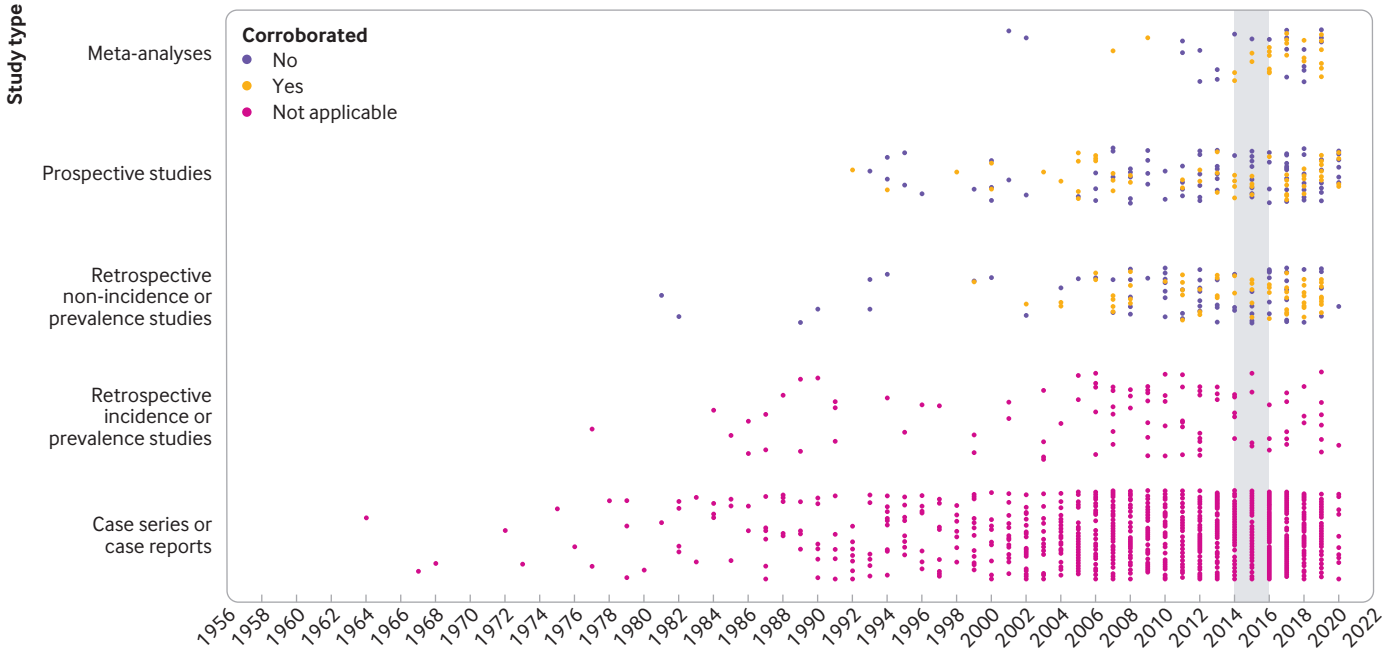

Relevant published studies identified for potential safety signals identified from the US Food and Drug Administration Adverse Event Reporting System in 2014-15, grouped by study type and corroboration of the FDA's regulatory action. Shaded bar denotes years 2014-15, when the potential safety signals were made public. Studies that corroborated the FDA's regulatory action, studies that did not corroborate the FDA's regulatory action, and descriptive studies that could not corroborate (not applicable) the FDA's regulatory action are indicated

13 led to drug safety communications, all supported solely by FAERS or other case reports.[5] The authors concede that an FDA action might reflect evidence that is not publicly available. Transparency of decision making is compromised, however, if decisions are based on confidential evidence.

International differences in post-market risk communications also expose limits to regulatory transparency. A comparison of safety warnings issued in the US, UK, Canada, and Australia between 2007 and 2016 found large discrepancies, with all countries issuing warnings for only 10% of identified safety concerns.[7] Boxed warnings and adverse events listed in product information also differ between countries.[8] The judgments underlying these differences warrant public discussion and explanation.

Dhodapkar and colleagues referred to safety signals as "resolved" if the FDA had taken regulatory action or judged none was needed. But are these signals really resolved? Meta-analyses of a systematic sample of regulatory safety warnings[9] and a systematic review of published research on these warnings[10] found modest and variable effects on prescribing. A multimodal analysis of FDA warnings on the sleeping pill zolpidem, for example, found only minor reductions in average dose, with women largely unaware of their increased risks.[11] This research strongly suggests a need to evaluate the effectiveness of safety related regulatory actions, and for further action if required, especially for serious harms.

Radical transparency about available evidence and the basis for regulatory judgments is needed

The public's right to know

Publication of safety signals is important, but this step is only the first towards transparency, with full public access needed to the evidence supporting all decision making, including decisions not to act. The covid-19 pandemic has exposed the tension underlying regulatory decisions and the public's right to know about serious risks associated with medical interventions. One key lesson learnt from the thromboembolic risks associated with the Covishield (ChAdOx1-S) covid-19 vaccine is the importance to public trust of full and timely disclosure of evidence on harms. Randomised trials comparing full risk disclosure with assurances of vaccine safety and effectiveness found that the assurances were linked to more mistrust and belief in conspiracy theories.[12] Søren Brostrøm, director of the Danish Health Authority, highlighted the need for radical transparency of regulatory decision making to address possible risks associated with covid-19 vaccines, including full public disclosure of available evidence, the extent of remaining uncertainty, and the judgments underlying decision making.[13]

This same tension exists more broadly in medicine safety. Given the widespread use of medicines, rare, serious harms are a pressing public health concern. Safety signals are an important step, but radical transparency about available evidence and the basis for regulatory judgments is needed to reduce harm caused by medicines, as is adequate follow-up to ensure safer use.

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Association between fluoroquinolones and hospital admission for suicidality

Wang J, Gagne JJ, Kattinakere-Sreedhara S, Fischer MA, Bykov K

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Study question What is the risk of suicidality associated with initiation of fluoroquinolones compared with azithromycin or combined trimethoprim and sulfamethoxazole?

Methods Information on the study population was obtained from the US IBM MarketScan database (1 January 2003 to 30 September 2015). Adults aged 18 years and older who had initiated an oral fluoroquinolone (see individual drugs in table footnote) after a diagnosis of pneumonia or urinary tract infection (UTI) were identified and compared with individuals who initiated a comparator antibiotic: azithromycin in the pneumonia cohort or combined trimethoprim and sulfamethoxazole in the UTI cohort. Participants were matched 1:1 within each cohort on a propensity score that included 57 baseline covariates. Primary outcome was admission to hospital or emergency department for suicidal ideation or self-harm within 60 days after initiation of treatment.

Study answer and limitations 275 521 of the propensity score matched pairs were included in the pneumonia cohort and 1 102 613 in the UTI cohort. During the 60 day follow-up, 181 events were observed in the pneumonia cohort and 966 in the UTI cohort. The adjusted hazard ratios for fluoroquinolones were 1.01 (95% confidence interval 0.76 to 1.36) versus azithromycin in the pneumonia cohort and 1.03 (0.91 to 1.17) versus trimethoprim-sulfamethoxazole in the UTI cohort. Results were consistent across sensitivity analyses and subgroups of sex, age, and history of mental disorders. As the data were not generated for research purposes, information was lacking on some patient characteristics that may affect the risk of suicidality. The billing code based outcome definition may underestimate the true incidence of suicidality. In addition, the results may not be generalizable to long term use of fluoroquinolones or to systemic fluoroquinolones.

What this study adds Initiation of fluoroquinolones was not associated with a substantially increased risk of admission to hospital or an emergency department for suicidality compared with azithromycin or trimethoprim-sulfamethoxazole. The absolute risk was low.

Funding, competing interests, and data sharing
Funded by the Division of Pharmacoepidemiology and Pharmacoeconomic, Brigham and Women's Hospital. No competing interests declared. No patient level data available.

Association between fluoroquinolone initiation and hospital admission or emergency department visit for suicidality

	Pneumonia cohort				Urinary tract infection cohort			
	Propensity score matching		High dimensional propensity score matching		Propensity score matching		High dimensional propensity score matching	
Analyses	Fluoroquinolones* (n=275 521)	Azithromycin (n=275 521)	Fluoroquinolones* (n=269 625)	Azithromycin (n=269 625)	Fluoroquinolones* (n=1 102 613)	TMP-SMX (n=1 102 613)	Fluoroquinolones* (n=1 098 770)	TMP-SMX (n=1 098 770)
No (%) of admissions	91 (0.03)	90 (0.03)	86 (0.03)	84 (0.03)	491 (0.04)	475 (0.04)	492 (0.04)	470 (0.04)
Risk/1000 patients	0.33	0.33	0.32	0.31	0.45	0.43	0.45	0.43
Hazard ratio (95% CI)	1.01 (0.76 to 1.36)	Reference	1.02 (0.76 to 1.38)	1 (Reference)	1.03 (0.91 to 1.17)	Reference	1.05 (0.92 to 1.19)	1 (Reference)

TMP-SMX=trimethoprim and sulfamethoxazole; CI=confidence interval.
*Ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, ofloxacin, gatifloxacin, norfloxacin, lomefloxacin, or besifloxacin.