

Inflammatory episodes and the triggering of acute vascular events

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Inflammation and vascular disease

- initial wave of studies reporting associations between serological markers of chronic infection and vascular disease
- more recent large scale work has shown generally weaker associations, but still a positive effect seen

Atherosclerosis

- atherosclerosis relatively benign
- the danger comes when plaques become unstable
- atherosclerotic plaques have many inflammatory components

Atherosclerosis

- inflammation may play a key role in destabilising vulnerable plaques
- Apo-E deficient mice, influenza A virus inoculation increased plaque inflammatory activity
- inflammatory markers predict outcomes in acute vascular events

The need for a better understanding

- Recent negative trials of antibiotics: no role for infection in vascular disease? Or.....
 - wrong drugs?
 - wrong targets?
 - wrong patients?
 - wrong time?
- Illustrate the need for a better understanding of the role of inflammation in vascular disease

Basic research: the stimulus

Vaccination of healthy volunteers induced a short-lived mild systemic inflammation that was associated with profound suppression of endothelium-dependent relaxation

Transient increase in myocardial infarction and stroke following infection but not vaccination

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Paddy Farrington, Open University
Patrick Vallance, University College London

Funded by the British Heart Foundation and MRC

Smeeth et al, NEJM 2004;351:2611-18

Objective

- to test the hypothesis of inflammation-induced fluctuation in vascular risk
- assess the risk of MI and stroke following influenza and other vaccinations or naturally occurring infections

Problem 1

- effect may be only a few days
- retrospective data on infectious exposures likely to be biased
- we don't know who is going to get an infection or who is then going to get an MI or stroke
- need a huge prospective study

Solution 1

Use computerised primary care data

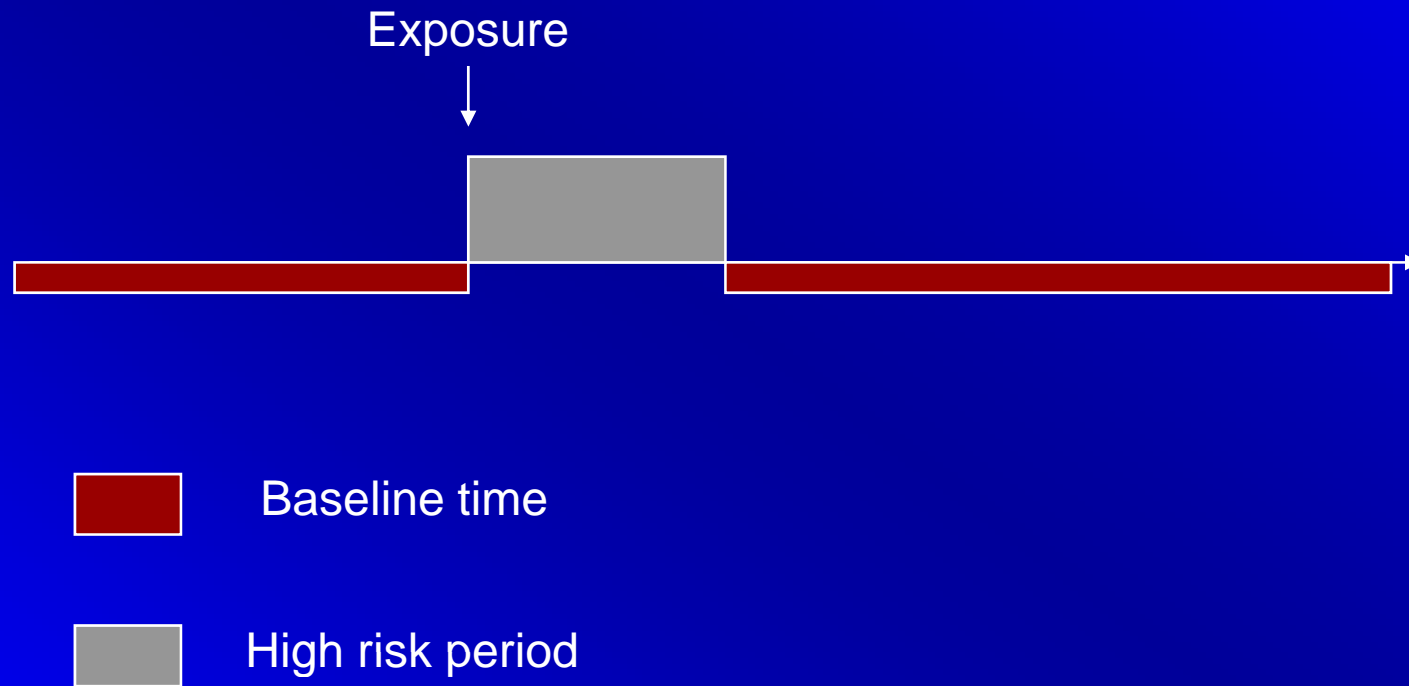
Problem 2

- people with and without diagnosed infections differ in ways that are difficult to measure and control
- selection bias and confounding may produce spurious results

Solution 2

Don't have a comparison group

Case-series method



Farrington CP. Biometrics 1995;51:228-235

The General Practice Research Database

- a collection of computerised primary care records
- around 400 general practices with a current combined list size of around 3 million patients
- data starts 1987 for a limited number of practices
- completely anonymous data

Data quality

- recorded diagnosis of MI for a sample of over 400 people confirmed in over 90% of cases
- similar for stroke: 89% validated against hospital records

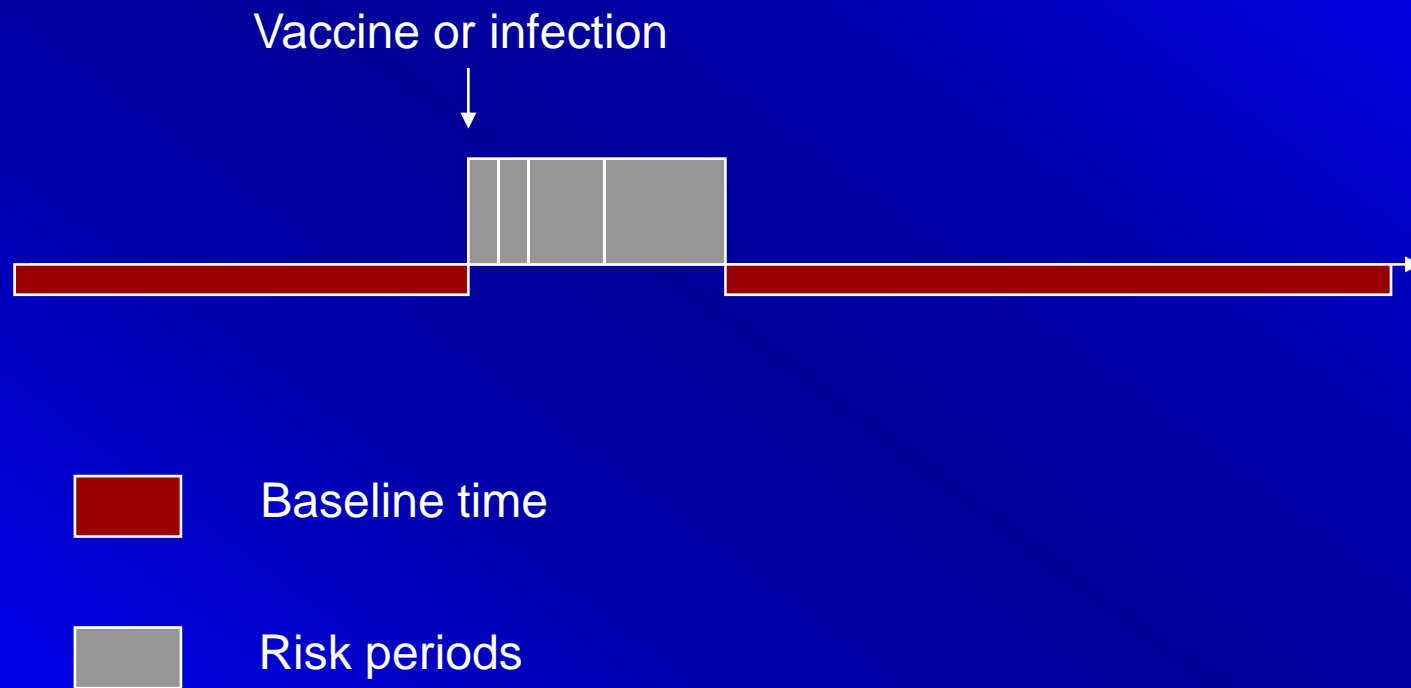
Cases

- 60,061 individuals comprised 53,709 with a first MI and 12,134 with a subsequent MI
- median age at MI=72.3 years
- 59.1% male
- mean observation duration 5.6 years

Exposures

- Respiratory tract infections: sufficient to be likely to cause systemic effects
- Urinary tract infections
- Common vaccines: influenza and pneumococcal

Case-series method



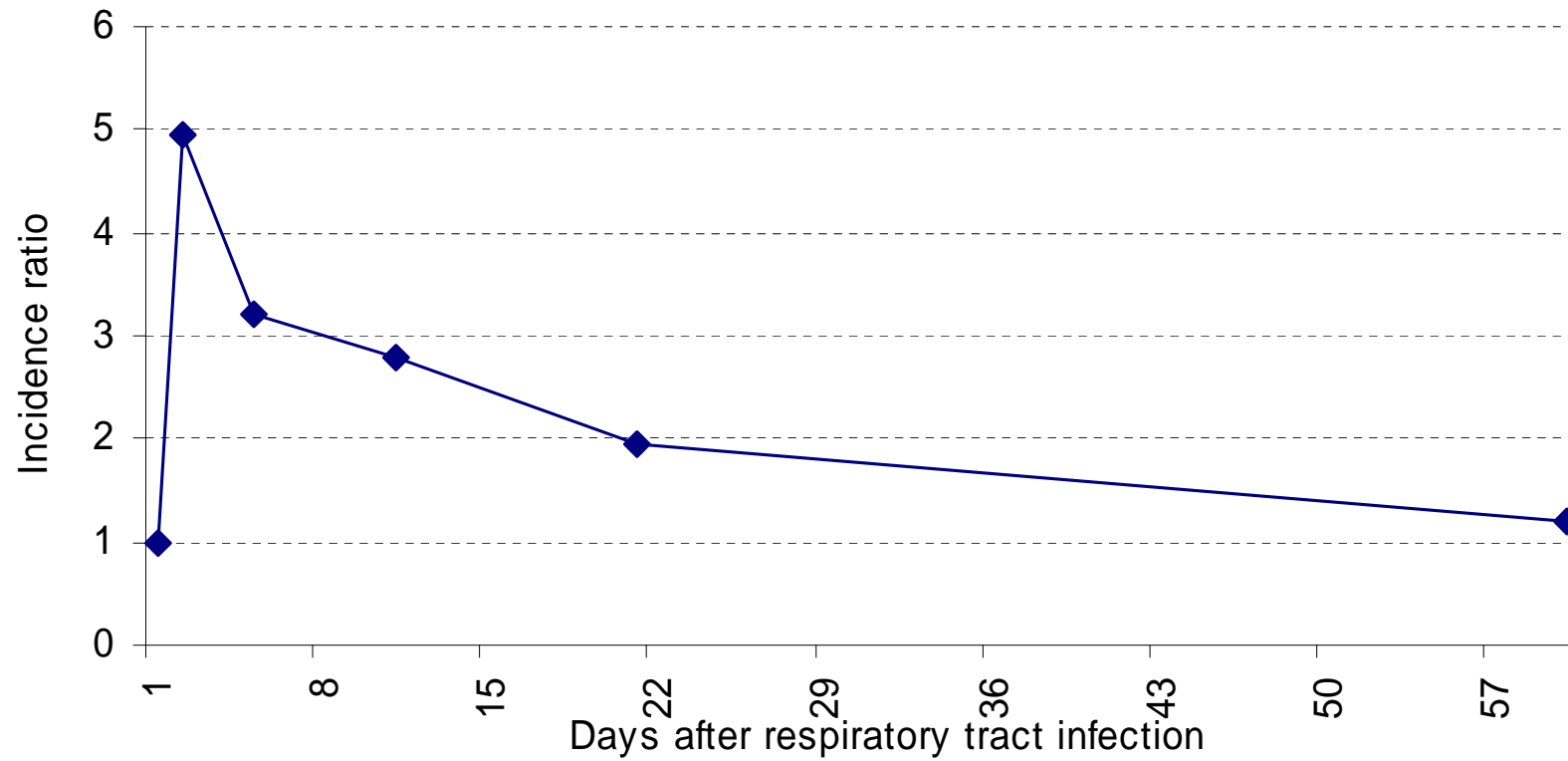
Time period (days following exposure)	Rate ratio and 95% CI
1-3	0.75 (0.60-0.94)
4-7	0.68 (0.56-0.84)
8-14	0.73 (0.63-0.85)
15-28	0.87 (0.79-0.96)

Rate ratio of first MI in risk periods following influenza vaccination (20,486 exposed cases)

Time period (days following exposure)	Rate ratio and 95% CI
1-3	4.95 (4.43-5.53)
4-7	3.20 (2.84-3.60)
8-14	2.81 (2.54-3.09)
15-28	1.95 (1.79-2.12)

**Rate ratio of first MI in risk periods following
respiratory infection (20,921 exposed cases)**

Incidence ratio of MI following respiratory tract infection



Time period (days following exposure)	Rate ratio and 95% CI
1-3	1.66 (1.28-2.14)
4-7	1.61 (1.28-2.02)
8-14	1.22 (1.00-1.49)
15-28	1.32 (1.16-1.52)

Rate ratio of first MI in risk periods following urinary tract infection (10,448 exposed cases)

Time period (days following exposure)	Rate ratio and 95% CI
1-3	3.19 (2.81-3.62)
4-7	2.34 (2.05-2.66)
8-14	2.09 (1.89-2.32)
15-28	1.68 (1.54-1.82)

**Rate ratio of first CVA in risk periods following
respiratory infection (22,400 exposed cases)**

Time period (days following exposure)	Rate ratio and 95% CI
1-3	2.72 (2.32-3.20)
4-7	2.12 (1.81-2.48)
8-14	1.89 (1.65-2.13)
15-28	1.71 (1.55-1.88)

Rate ratio of first CVA in risk periods following urinary tract infection (14,603 exposed cases)

Venous thromboembolism

- If the arterial effect is due to endothelial activation, we should see a similar effect for venous thromboembolism (VTE)
- Deep vein thrombosis (DVT)
- Pulmonary embolism (PE)

Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting

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Patrick Vallance, University College London

Funded by the MRC

Smeeth et al, Lancet 2006;367:1075-1079

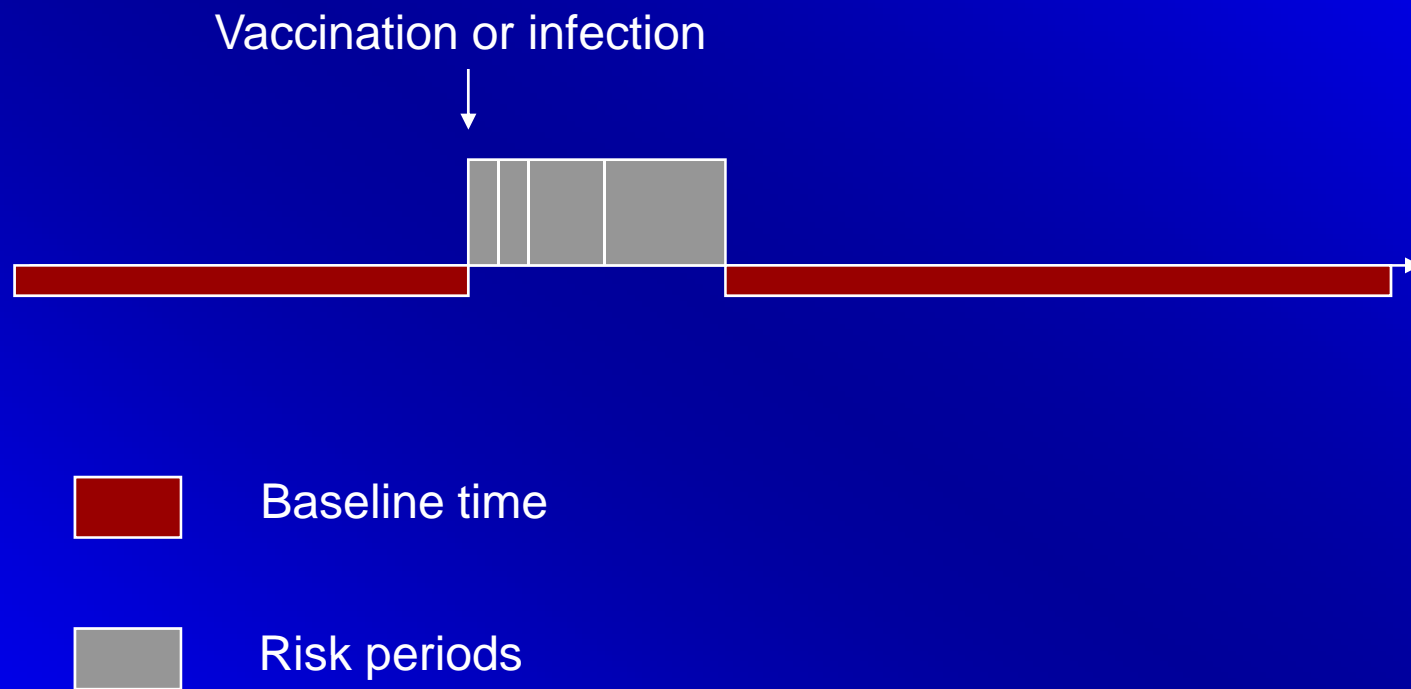
Virchow's triad

- venous stasis
 - increased coagulability of the blood
 - damage to the vessel wall
- ➔ this could include factors that affect endothelial function

Analysis

- DVT and PE analysed separately
- infections and vaccinations
- risk periods in two week blocks then in months, through to 1 year

Case-series method



Time period in weeks	Cases	Rate ratio and 95% CI
1-2	70	1.96 (1.5,2.5)
3-4	58	1.65 (1.3,2.1)
5-8	110	1.66 (1.4,2.0)
9-12	74	1.21(1.0,1.5)
13-26	267	1.42(1.2,1.6)
27-39	166	1.11(0.9,1.3)
40-52	148	1.13(1.0,1.3)
baseline	2652	1.00

Rate ratio of first DVT in risk periods following respiratory infection

Time period in weeks	Cases	Rate ratio and 95% CI
1-2	23	2.11 (1.38,3.23)
3-4	23	2.11 (1.38,3.23)
5-8	38	1.83 (1.31,2.57)
9-12	26	1.38 (0.92,2.06)
13-26	74	1.27 (0.99,1.64)
27-39	52	1.15 (0.86,1.54)
40-52	46	1.16 (0.85,1.58)
baseline	752	1.00

Rate ratio of first PE in risk periods following urinary infection

Conclusions 1

- two different infectious processes are associated with a transient increased risk of both arterial and venous events
- lends strong support to the concept that systemic inflammation *per se* alters the probability of occurrence of a vascular event
- may be due to short-term alteration of endothelial function or other rapid changes in plaque composition or white cell activation or simply haemodynamic stress

Conclusions 2

- strongly suggest a generic effect of infection (or inflammation) on vascular events
- implications:
 - history of infection in someone with a suspected event
 - new or existing preventative measures at inflammatory times?

