education

FROM THE JOURNALS Edited highlights of weekly research reviews

Cause for optimism with cancer treatments

Bowel cancer and breast cancer remain common causes of death. Two new studies provide cause for optimism in hard to treat subsets of both cancers.

Women with triple-negative breast cancers tend to have a poor prognosis as the cancers are aggressive and unresponsive to standard therapies as they lack oestrogen, progesterone, and human epidermal growth factor receptors. In a new trial, first stage (neoadjuvant) treatment with pembrolizumab (a programmed death 1 (PD-1) inhibitor) plus chemotherapy followed by post-treatment (adjuvant) pembrolizumab significantly improved overall survival compared with neoadjuvant chemotherapy alone in early onset, high risk, triple-negative breast cancer (estimated overall survival at 5 years 86.6% *v* 81.7%).

Among people with metastatic colorectal cancer (mCRC), around 5% have mismatch repair deficient (dMMR) and high microsatellite instability (MSI-H) tumours, which are more likely to be sensitive to immune checkpoint inhibition but less likely to respond to standard (fluoropyrimidine based) chemotherapy and non-immunologic targeted therapies. In a phase 3, multinational, randomised trial, progression-free survival at two years was significantly better with two immunotherapy drugs, nivolumab plus ipilimumab, than with chemotherapy (72% *v* 14%).

N Engl J Med doi:10.1056/NEJMoa2409932, doi:10.1056/NEJMoa2402141

Traditional Chinese medicine for intracerebral haemorrhage

Chinese herbal medicine is widely used across the world, but evidence of efficacy and safety is often lacking. This well conducted, pragmatic, multicentre, randomised trial at 26 hospitals in China compared an oral solution containing a mix of herbs—FYTF-919 (Zhongfeng Xingnao)—with placebo in 1648 patients with moderate to severe symptomatic spontaneous intracerebral haemorrhage (confirmed by brain imaging).

The herbal medicine was given within 48 hours of the onset of symptoms that resulted in moderate to severe neurological impairment. The rationale is that FYTF-919 can enhance resorption of a haematoma and reduce neuroinflammation. However, after three months, there was no difference in functional recovery, survival, or health-related quality of life between the treatment and placebo groups and no difference in adverse effects. All existing and new therapies on offer to patients should be subject to this kind of robust inquiry whatever their provenance.

Lancet doi:10.1016/S0140-6736(24)02261-X

Treat the patient not the number?

Being admitted to hospital is bad for your blood pressure: 70% of patients have asymptomatic blood pressure elevations, with at least one systolic blood pressure reading over 140 mm Hg. Clinicians often prescribe antihypertensive medication "as-needed" or as a one-time dose, but there's a risk of inducing ischaemia if blood pressure is lowered rapidly, especially in older patients.

This retrospective cohort study of over 133 000 US veterans (96% men, mean age 71 years) who were admitted to hospital for a minimum of three days (but didn't need intensive care or surgery) and received at least one blood pressure lowering drug within 24 hours of admission found that the as-needed group had a greater risk of a rapid drop in blood pressure, acute kidney injury and a 1.69-fold higher rate of a composite outcome of stroke, myocardial infarction, or death compared with non-users. We need a much wider prospective trial to determine when lowering blood pressure causes more harm than good.

JAMA Intern Med doi:10.1001/jamainternmed.2024.6213

Players not pawns

Burnout and poor workforce retention are major problems in health care. Is "taking back control" the answer? This cross sectional US study of over 2000 doctors working in large group practices used a novel measure of burnout—intent to reduce working hours and intent to leave their current job.

More than 60% of those surveyed said they had adequate control over patient load, composition of their team, clinical schedule, and overall workload. Even after adjusting for personal and professional characteristics, poor control in each of these areas was independently associated with burnout. Poor control over workload was independently associated with intention to reduce working hours. This type of study can't prove causality, and doctors in the large practices surveyed may not be typical of smaller practices. But no one likes to feel like a powerless pawn.

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Evidence for local anaesthetic transperineal biopsy versus transrectal prostate biopsy

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CPD READING
0.5 HOURS

WHAT YOU NEED TO KNOW

- Prostate biopsy under local anaesthetic can be performed via the transrectal (TRUS) or transperineal (LATP) routes. Both use transrectal ultrasound
- Each prostate biopsy technique has pros and cons, including differences in targeting multiparametric MRI visible lesions, potential complications, patient tolerability, expense, and time to undertake the procedure in the outpatient clinic
- Three randomised controlled trials show no difference for infection or overall cancer detection between TRUS and LATP. However, these trials were underpowered to detect a difference, mainly because of the better than expected performance of TRUS in both categories. A further larger trial is awaited

Prostate cancer is usually diagnosed using image guided needle biopsy. Approximately 70 000 such biopsies are performed annually in the UK,[1] but these numbers have fallen since the widespread introduction of prostate multiparametric magnetic resonance imaging (mpMRI) scanning as a pre-biopsy investigation for men suspected to have prostate cancer.[2 3] Initial suspicion normally arises following blood test results that show a raised level of prostate specific antigen (PSA) and/or an abnormal prostate examination, which are usually undertaken as part of case finding or opportunistic screening.[4] However, prostate biopsies are an expensive intervention and have significant side effects for patients, and uncertainty persists on the need for further biopsies in the case of negative results.

Over the past three decades, prostate biopsy techniques have been increasingly refined, centring around transrectal ultrasound (TRUS), image guidance of biopsy needle placement, use of pre-biopsy mpMRI, and needle guidance access systems. The past five years have seen a gradual trend away from transrectal biopsy towards local anaesthetic transperineal biopsy (LATP), precipitated primarily by concerns about the infection risk of transrectal biopsy, along with the perceived superiority of transperineal biopsy in targeting mpMRI visible lesions.[5] Transperineal access systems have removed the need for either a large fixed stepper system or "double free-hand" approaches, as the needle position can be fixed relative to the ultrasound probe in a "single free-hand" manner (fig 1), making the biopsy technically easier and less cumbersome. Additionally, in the UK, partly in response to raised public awareness of the diagnostic process in prostate cancer,[6] there has been central funding for training and leadership to facilitate a transition from transrectal to transperineal biopsy.

In England, figures from Hospital Episode Statistics show that LATP rates have been gradually increasing since 2014 (fig 2).[1 7] The covid-19 pandemic accelerated the transition from TRUS to LATP when early evidence suggested presence of the virus in faeces.[8] These factors have contributed to LATP exceeding TRUS in 2020. Despite this, prior to 2024 no randomised control trial (RCT) evidence found in favour of either technique, with all publications presenting observational data.[9] In this article, we outline the current uncertainty regarding LATP prostate biopsy.

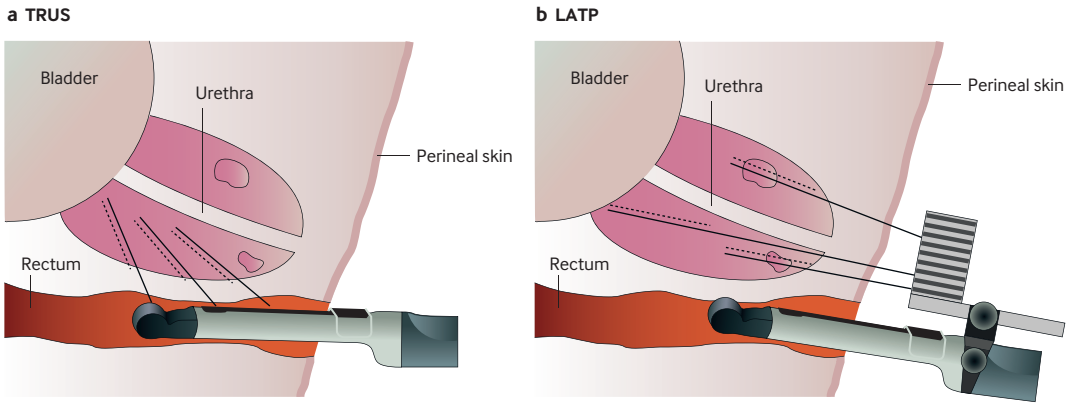

Fig 1 | (A) Transrectal ultrasound (TRUS) guided prostate biopsy and (B) Local anaesthetic transperineal (LATP) prostate biopsy differ by route of entry, being either transrectal (TRUS) or transperineal (LATP). Both involve a transrectal ultrasound probe and insertion of core biopsy needles into the prostate for diagnosis of prostate cancer

What is the evidence of uncertainty?

A summary of the recommendations from existing international guidelines is presented in table 1. Several observational cohort studies initially suggested that LATP might be superior to TRUS biopsy in detecting clinically significant prostate cancer, while reducing infection risk.[9] We highlight the ongoing uncertainty in some key areas and evidence related to RCTs in table 2.

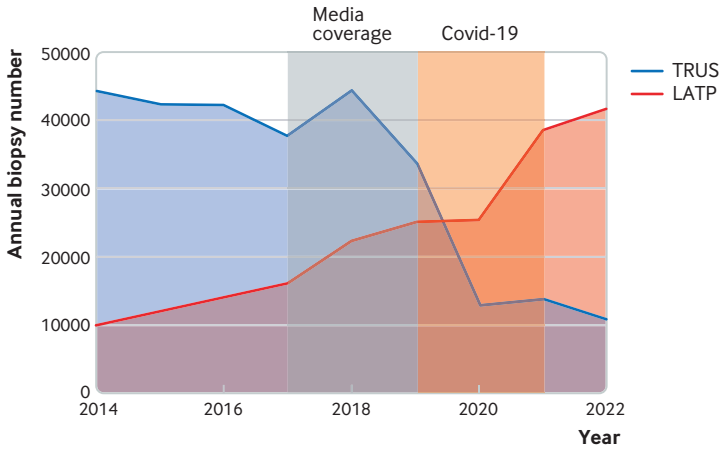

Fig 2 | Changes in numbers of prostate biopsies performed since 2014. Hospital Episode Statistics data for England only, accessed from National Prostate Cancer Audit. Shaded areas correspond to external events influencing biopsy numbers, such as the 'Fry/Turnbull' effect[6]

Table 1 | Guideline recommendations on local anaesthetic transperineal prostate biopsy

Guidelines	Title	Summary recommendations
National Institute for Health and Care Excellence	Transperineal biopsy for diagnosing prostate cancer (DG54) 1 June 2023[10]	1.1 LATP prostate biopsy using the freehand needle positioning device PrecisionPoint is recommended as an option for diagnosing prostate cancer 1.2 Uncertainty regarding other devices but expected to be similar to Precision Point so same recommendation, eg, EZU-PA3U device; Trinity Perine Grid; UA1232 puncture attachment 1.3 Encouragement to participate in research, including the TRANSLATE trial RCT 1.4 Insufficient evidence to recommend double freehand LATP
European Association of Urology	Prostate Cancer (March 2023)[11]	Perform prostate biopsy using the transperineal approach owing to the lower risk of infectious complications. Strength of recommendation: "strong"*
American Urology Association	Prostate Cancer Guidelines[12]	Clinicians may use either a transrectal or a transperineal biopsy route when performing a biopsy. Evidence level: "grade C"

*European Association of Urology guideline notes that the evidence supporting this summary statement is weak

Table 2 | Current level 1 evidence comparing LATP and TRUS biopsy

Name of trial	Location	ClinicalTrials.gov	Participants	Primary outcome *(Finding)*	Study reporting date
ProBE-PC[13]	New York	NCT04081636	718 Mixed biopsy naïve and previous negative biopsy; Mixed MRI/no MRI	Infection and bleeding within 30 days *(No difference)*	February 2024
PCORI/ Prevent	New York	NCT04815876	658 biopsy naïve,1300 mixed AS or previous negative biopsy; Mixed MRI/no MRI	Infection *(No difference)*	February 2024 April 2025
Perfect[14 15]	France	NCT05069584	270 Biopsy naïve, all MRI	Detection of csPCa *(No difference)*	April 2024

AS = active surveillance. MRI = magnetic resonance imaging. csPCa = clinically significant prostate cancer

Diagnostic accuracy

Observational studies have suggested that LATP may have a higher cancer detection rate compared with TRUS biopsy, particularly for tumours located in the anterior or apical part of the prostate gland; however, meta-analyses from 2023 showed conflicting results,[16 17] and the magnitude of this potential advantage for different anatomical locations in the prostate remains unclear.

More research is needed to directly compare the diagnostic accuracy of the two biopsy methods in a randomised controlled population. Studies presenting LATP data represent practice from early adopters, who had a particular interest in prostate cancer diagnostics. It may therefore be inappropriate to compare these results with longer term TRUS biopsy series, which have often been performed by urological trainees, nursing colleagues, and general urologists. In 2024, one RCT (the Perfect trial) investigated diagnostic yield as a primary outcome and reported an inferior detection rate of clinically significant prostate cancer (csPCa) from biopsy of posterior lesions on MRI with LATP versus TRUS biopsy.[14] A further RCT found no difference in detection of csPCa when investigated in a secondary outcome analysis.[18]

Infection risk

Transrectal biopsy requires passage of a needle biopsy through the rectal wall. In contrast, transperineal biopsies enter through the perineal skin. The rates of infection (such as urinary tract infection, prostatitis, gastrointestinal infections, and sepsis) resulting from the two biopsy approaches are variable and are dependent on the geographical location of the cohort, population demographics, and the local degree of antibiotic resistance, particularly to quinolones. This is largely because of increased use and higher rates of quinolone resistance in the Indian subcontinent. Outside metropolitan areas the infection rates with TRUS biopsy, particularly when clinicians use rectal swabs and antiseptic preparation such as iodine, may be much lower than the 5% rate quoted in some of the literature. Case series show low rates of demonstrable sepsis after LATP, at less than 1%.[19-22] Importantly for antibiotic stewardship, LATP may enable equivalent or lower infection rates without the need for antibiotic prophylaxis.[23 24]

The Probe-PC,[13] Prevent (PCORI),[18] and Perfect (CCAFU-PR1)[14] randomised controlled trials did not show any difference in composite infection outcomes between the two approaches, although the studies were underpowered to detect sepsis, with minimal events in either group.[13 18]

Patient tolerability

LATP biopsy has been reported to be less comfortable for patients compared with TRUS biopsy.[25 26] However, patient experiences vary, and factors such as expertise of the operator can influence overall patient experience. A prospective comparative study using a visual analogue pain scale found no overall difference between the two approaches, but highlighted increased pain during placement of local anaesthetic in LATP.[25] This

Table 3 | Ongoing randomised controlled trials comparing LATP and TRUS biopsy

Name of trial	Location	ClinicalTrials.gov	Participants	Primary outcome *(Finding)*	Recruitment completion date*
PREVENT2*	New York	NCT04815876	1300 Mixed AS or previous negative biopsy; Mixed MRI/no MRI	Infection	April 2025
TRANSLATE[28]	UK	NCT05179694	1042 Biopsy naïve, all MRI	Detection of Gleason pattern 4 PCa	Sept 2023
Hong Kong†	Hong Kong	NCT04108871	180 Biopsy naïve, no MRI	Detection of PCa	April 2022

*According to clinicaltrials.gov

†Trial complete but awaiting publication (author communication).

AS=active surveillance. PCa=prostate cancer

study also found no difference in urinary symptoms or retention. The Probe questionnaire was developed to provide a comprehensive assessment of patient acceptability of transrectal biopsy.[27] To our knowledge, only one study has attempted comprehensively to assess patient tolerability following LATP. This highlighted an important minority of patients who described the procedure as a moderate or major discomfort, with some patients expressing preference for the left lateral position used for TRUS rather than the lithotomy position required for LATP (45% of men in this study had previously undergone TRUS).[19] The Prevent trial also assessed tolerability using a Likert scale (0-10) and reported a 0.6 "adjusted increase" in peri-procedural pain with LATP. Patient tolerability needs to be assessed in a robust comparative study.[28] Nevertheless, we believe that most of the physical discomfort experienced relates to the placement of the rectal ultrasound probe, which is common to both approaches, and we therefore await the comparative data.

Cost and resourcing

The cost effectiveness of LATP versus TRUS biopsy is important to consider. The availability of equipment, local expertise, time taken for the procedure, and healthcare resources may influence the practicality of adopting LATP on a broader scale. When using a transperineal access system (single freehand), LATP biopsy requires use of additional equipment and therefore costs more. Some evidence also suggests that LATP biopsy takes longer than TRUS biopsy.[29] However, these extra investments in LATP may remain cost effective as this approach may reduce the need for antibiotics. The health economic analysis within the Translate trial[28] will provide the first comprehensive evidence on this.

WHAT PATIENTS NEED TO KNOW

- If referred for investigation of possible prostate cancer, most patients will require a prostate biopsy, usually after a pre-biopsy mpMRI scan
- Transrectal and transperineal biopsies can both be performed under local anaesthetic in the outpatient clinic
- The two different approaches have risks and benefits and, so far, no high quality evidence shows that either approach is definitively superior to the other

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

The chairman of our local Oxford Prostate Cancer Support Group (OPCSG; https://www.opcsg.org/) is a prostate cancer survivor, a co-investigator in the Translate trial, and a co-author of this article. He helped with the design of the Translate trial, including the primary and secondary outcomes, and generating survey data about the key areas of concern for men undergoing prostate biopsy

EDUCATION INTO PRACTICE

- How would you communicate the risks and benefits of the different approaches to prostate biopsy?
- What are the priorities for men undergoing the prostate cancer diagnostic process? (eg, ruling in/out cancer, avoiding infection, avoiding discomfort, etc)
- Are there any other areas of practice where clinicians may advocate one diagnostic or treatment option over another in the absence of high quality evidence?

Ongoing research

Five RCTs registered at clinicaltrials.gov (PROBE, PREVENT, PERFECT, TRANSLATE, and the Hong Kong trial) directly compare LATP with TRUS biopsy (tables 2 and 3). These have and will provide important data regarding key diagnostic and side effect outcomes, as well as cost effectiveness analysis of the two methods of prostate biopsy.

What should we do now?

No high quality evidence favours either option; therefore it seems appropriate to maintain equipoise regarding the optimal technique for prostate biopsy until the full results of the current RCTs are available.[30,31] We need to be careful. There are high profile examples of the field moving towards a preferred option despite the absence of comprehensive data. For example, da Vinci robotics have been widely adopted in prostatectomy surgery, despite only one large RCT performed in over two decades of its use, which showed no evidence of a difference from open surgery in key patient related outcomes.[32]

When deciding which prostate biopsy technique to use, we suggest clinicians weigh the evidence and consider the technique familiar to their unit and the patient's preferences. It is possible, as the evidence continues to emerge, that clinicians may choose to offer LATP for patients with a history of urinary sepsis or immune compromise as well as those with anterior prostate lesions on diagnostic MRI.

Recent guidance from the National Institute for Health and Care Excellence included a summary recommendation (*Recommendation 1.4*[10]) for urology units in the UK to support recruitment to the Translate trial. Updates to guidance are likely in due course when we have evidence based answers to these important questions.

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STATE OF THE ART REVIEW

Acute respiratory distress syndrome

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This is a summary of Clinical Review *Acute respiratory distress syndrome*. The full version can be read here: https://www.bmj.com/content/387/bmj-2023-076612

CPD READING
0.5 HOURS

Acute respiratory distress syndrome (ARDS) is characterised by severe, diffuse inflammatory injury to the lung parenchyma resulting from a predisposing risk factor (for example, pulmonary or non-pulmonary infection, trauma, aspiration, or shock).[1] Before covid-19, ARDS was estimated to occur in approximately 10% of critically ill patients, with a high mortality rate of approximately 30-50%.[2] The covid-19 pandemic increased the incidence of ARDS,[3 4] although its exact impact on the incidence and outcomes of ARDS requires further study. Nevertheless, ARDS remains a highly fatal condition with long term sequelae.[5] Optimising intensive care through appropriate ventilation and fluid management is still the most effective way to reduce the mortality and complications of ARDS.[6 7]

Historical perspective and updated definition

ARDS was first described in a case series in 1967.[9] Defining characteristics of the syndrome were the occurrence of tachypnoea, hypoxaemia, and reduced lung compliance after a predisposing insult. The authors also noted patchy bilateral infiltrates on chest radiography that closely resembled hydrostatic pulmonary oedema. Autopsy samples showed inflammation, alveolar oedema and collapse, interstitial oedema, and hyaline membranes.[9] In this series the level of respiratory support needed was not considered a defining feature of the syndrome.[9]

WHAT YOU NEED TO KNOW

- ARDS is a critical illness syndrome with high morbidity and mortality, for which the most effective treatment remains optimisation of intensive care, including appropriate ventilation and fluid management
- No drug therapies have consistently shown benefit in all cases of ARDS. Reversible contributors should be identified and treated first, particularly when the cause is infection
- Criteria for defining ARDS have changed over time. A 2023 consensus conference proposed an expanded definition, which is likely to change the epidemiology of the condition by enabling diagnosis in settings where technological constraints were previously a barrier

The criteria for defining ARDS have changed, with varying degrees of importance placed on the role of positive pressure ventilation. In 1988 Murray and colleagues introduced the Lung Injury Score.[10] This score is calculated on the basis of a four point score of the severity of radiographic abnormality, hypoxaemia, amount of positive end expiratory pressure (PEEP) in mechanically ventilated patients, and lung compliance when measured. Any combination of severe abnormalities resulting in a score >2.5 constitutes ARDS under this definition, even in the absence of positive pressure ventilation or a lung compliance measurement.[10] In 1994 the American European Consensus Conference (AECC) definition introduced "acute lung injury" to describe patients with less severe hypoxaemia. This specified that the parenchymal injury must be acute, that oedema cannot be the result of elevated left atrial pressure, that severity should be stratified by the ratio of partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) (with the term "ARDS" reserved for only more severe hypoxaemia with PaO_2/FiO_2 ≤200 mm Hg) regardless of the presence or absence of applied PEEP.[11] The 2012 Berlin definition introduced a conceptual model of ARDS, specified the timeline of "acute" parenchymal injury to be within seven days, eliminated acute lung injury in favour of mild, moderate, and severe ARDS, and required that ≥5 cm H_2O of PEEP be applied by invasive or non-invasive mechanical ventilation.[12]

A consensus conference in 2023 proposed an expanded global definition of ARDS (see fig 1, online) that includes patients receiving high flow nasal oxygen (HFNO), allows for the diagnosis of ARDS using pulse oximetry without the requirement for an arterial blood gas, allows thoracic ultrasonography in the absence of availability of chest radiography, and formally incorporates the Kigali modification of the Berlin definition for resource limited areas.[8 13] The rationale for this expansion includes that the clinical use of HFNO is the preferred mode of support for some patients with hypoxaemia and bilateral opacities who would previously have been managed with an endotracheal tube and that the Berlin definition restricts the diagnosis of ARDS to settings in which advanced diagnostic and support modalities are available.[8 14-16] Limitations of the global definition include lack of validation in large cohorts of patients and ongoing uncertainty about what constitutes the "gold standard" for identifying ARDS.[17] However, most patients not receiving positive pressure ventilation continue to fulfil criteria for ARDS after initiation of ventilation.[18] In addition, expanding the definition of covid-19 related ARDS to include patients being treated with HFNO did not negatively affect the definition's predictive validity for mortality.[19]

Epidemiology

Population based studies since the publication of the AECC definition have varied widely in their estimates of the incidence of ARDS, ranging from 3.65 to 78.9 per 100 000 person years.[20] Hospital based studies similarly vary, with estimated incidence among admissions ranging from as low as 1.3% to as high as 19%.[20 21] Some studies have found that mortality related to non-covid ARDS has remained relatively static over time at about 30-35% for mild ARDS and 45-50% for severe ARDS,[2 20 21 23-28] despite changes in standard management. However, other studies have found an overall decrease in mortality rates for ARDS.[29-31]

The covid-19 pandemic altered the epidemiology of ARDS, with one estimate indicating a 10-fold increase in the incidence of ARDS with covid-19 in the US from March 2020 through February 2022.[38] Estimates of mortality from covid-19 ARDS vary widely by region, but a global pooled estimate found that covid-19 ARDS has a mortality rate of 39%, similar to that of non-covid ARDS,[2 41] which is in keeping with estimates from several other studies.[19 39 40] How the incidence and outcomes of non-covid ARDS changed during the covid-19 pandemic is not well understood.

The new global definition of ARDS will undoubtedly affect the epidemiology of ARDS. Because of the formal adoption of the Kigali modification,[13] diagnosing ARDS will be feasible in settings where diagnosis was previously not possible because of technological constraints.[8 15 44]

Risk factors

Risk factors for the development of ARDS can be considered in two categories: proximal risk factors (that is, those that predispose to the development of ARDS within the traditional seven day window) and background risk factors including demographics, medical comorbidities, and environmental exposures.

Proximal risk factors

The most common proximal cause of ARDS is infection, either pulmonary or non-pulmonary, with aspiration, multiple transfusions, trauma, and pancreatitis as less common causes in most epidemiological studies.[2 25 29 34 46 47] Some studies have found that the overall incidence of ARDS associated with trauma has decreased,[48 49] although others have found no change.[50] Few studies have looked at the incidence of and risk factors for ARDS outside high income countries, but the limited existing data suggest that infection remains the most common predisposing risk factor in low and middle income countries[13 23 52]; however, pathogens such as plasmodium species, dengue virus, and leptospirosis are more common in these settings than in high income countries.[53-56] Trauma is also a more common risk factor in low and middle income countries than in high income countries,[13 57] and strategies to limit transfusion related acute lung injury (TRALI) have not been implemented in many low/middle income countries.[51]

Background risk factors

Demographics

Patient specific and population specific factors also inform the risk of development of ARDS. Before the covid-19 pandemic, data about the role of older age, race and ethnicity, and sex in both the development of and outcomes from ARDS among people at risk were conflicting.[32 33 58-67] In covid-19, older age and male sex were clear risk factors for the development of severe disease, including ARDS.[43 68-72] The influence of race and ethnicity on the development of ARDS related to covid-19 is less clear after adjustment for other factors,[43 68 73 74] perhaps because the effect of race depends in turn on other factors such as regional differences in access to healthcare and risk of exposure.[75] Beyond traditional demographic considerations, evidence also suggests that genetic factors contribute to the risk of developing ARDS and its outcomes.[76]

Comorbidities

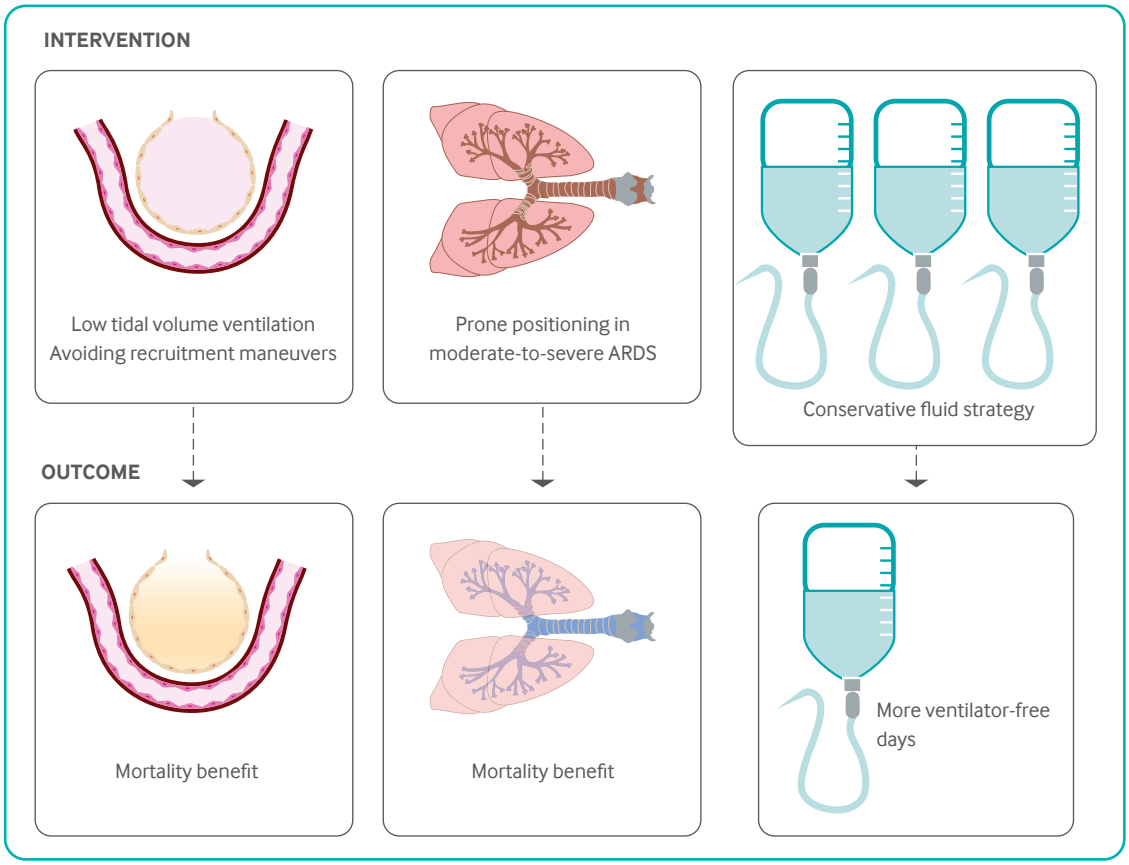
Several medical comorbidities are more common among patients with ARDS than in the general population. For example, 21% of patients in the LUNG-SAFE study had diabetes compared with an age standardised global prevalence of <10%.[2 77] The prevalences of chronic obstructive pulmonary disease and chronic heart failure among patients in LUNG-SAFE were similarly approximately twice the global prevalence.[2 78 79] Chronic medical comorbidities, especially malignancy and immunosuppression, are known risk factors for adverse outcomes from critical illness.[80-84] Diabetes and obesity merit particular consideration for non-covid related versus covid related ARDS because of their seemingly divergent effects on outcomes by cause.

Environmental exposures

Certain exposures, such as to air pollution, alcohol, and cigarette smoke, also contribute to the risk of ARDS.[106] An emerging connection has been identified between risk and outcomes of ARDS and ambient particulate matter and gaseous pollutants,[107-110] including adverse outcomes from covid-19.[111-114] Chronic alcohol use also predisposes to both non-covid ARDS and covid-19 ARDS.[115-118] Cigarette smokers are at risk for adverse outcomes of ARDS at comparably lower severity levels than are non-cigarette smokers.[106 119 120] Emerging evidence on the role of tobacco smoking in covid-19 suggests that cigarette smoking increases the risk of severe covid-19 and death, although the incidence of initial SARS-CoV-2 infection among smokers may be lower.[121-123] Overall, the predisposition to developing ARDS and related adverse outcomes is complex and depends on the interplay among personal susceptibility, individual exposures, population level risk factors, and the environment.

Pathology

The pathology of ARDS is classically described as a diffuse alveolar damage (DAD) pattern characterised by protein rich intra-alveolar oedema, hyaline membrane formation,



Interventions to improve outcomes in acute respiratory distress syndrome (ARDS). Interventions that have been shown to improve clinical outcomes in ARDS include lung protective low tidal volume plateau pressure limited ventilation, prone positioning for moderate to severe hypoxaemia, and fluid conservative therapy once shock is resolved

neutrophil infiltration, and alveolar haemorrhage.[12] Animal models of ARDS often seek to replicate this pattern.[180] DAD is not universal among patients with clinical ARDS, however,[181] as acknowledged in the recently proposed global definition of ARDS.[8] One challenge for better understanding the spectrum of histological manifestations of ARDS is that few patients undergo tissue sampling,[182] and lung biopsy is often restricted to those with unresolving ARDS or ARDS of unknown cause.[183] Other studies of the pathology of ARDS rely on autopsy series, which may not reflect the histological changes in non-fatal cases.[181 184] DAD is more common among patients with severe ARDS and is associated with worse respiratory system compliance, oxygenation, and overall illness severity, including higher mortality.[185] Clinical characteristics do not consistently predict the presence of DAD,[185 186] however, and DAD is present in only approximately half of cases of severe ARDS.[181 183 185] As histological changes in ARDS are not necessarily uniform, lung biopsy might not capture DAD in every case in which it is present, making consistent clinical correlations even more difficult. Better methods for identifying clinical correlates of histological ARDS findings could be useful in identifying effective therapies and require further study.[188]

Management

Critical care interventions

The cornerstone of ARDS management is effective comprehensive critical care interventions (table 1, online), many of which, in contrast to pharmacological interventions, have consistently been associated with reduced mortality and duration of mechanical ventilation (figure). Thus, clinicians need to recognise ARDS early and appropriately implement mortality reducing interventions such as lung protective ventilation and prone positioning.[201 202] Lung protective ventilation with low tidal volume (6 mL/kg predicted body weight) and a plateau airway pressure below 30 cm H_2O reduces mortality from ARDS and should be universally applied in patients with known or suspected ARDS.[203] Inconsistent application of low tidal volume ventilation results in meaningful differences in adverse outcomes such as prolonged intubation and mortality.[187] Although this would seem to be a pulmonary specific intervention, the application of lower tidal volumes also attenuates the systemic inflammatory response.[204 205] Ventilator management of tidal volumes should not meaningfully differ in patients with covid-19 ARDS.[206]

Low tidal volume ventilation does not entirely mitigate the risk of ventilator induced lung injury. A trial of ultra-low tidal volume ventilation facilitated by extracorporeal removal of carbon dioxide found no mortality benefit.[198] This trial had several limitations and a more targeted trial is needed. Other strategies for improved ventilator management, such as limiting driving pressure, varying tidal volumes to avoid possibly injurious effects of consistent tidal volume ventilation,[208] and personalising PEEP to surrogate

measurements of pleural pressure or radiographic features, have also not improved mortality in clinical trials.[189] Aggressive recruitment manoeuvres using sustained delivery of very high PEEP are injurious and should be avoided.[209-211]

ARDS can sometimes be managed with non-invasive respiratory support. HFNO in patients with acute hypoxaemic respiratory failure (AHRF), some of whom met clinical criteria for ARDS,[8] reduced mortality in a large clinical trial compared with non-invasive ventilation (NIV) via facemask or conventional oxygen therapy (COT).[193] A post hoc analysis of this trial found possible evidence of harm from NIV, but current evidence does not support extrapolation of these results to immunocompromised patients.[194 195 200 212] Before the covid-19 pandemic, a systematic review and meta-analysis including 3804 participants with AHRF found that helmet and facemask NIV were associated with a lower risk of mortality compared with COT, whereas HFNO was not.[213] This meta-analysis included participants with exacerbations of chronic obstructive pulmonary disease or heart failure as their cause of respiratory failure, although trials primarily focused on these causes were excluded. A more recent systematic review and meta-analysis of non-invasive oxygen in AHRF, including studies of participants with covid-19 respiratory failure and excluding studies focused on participants enrolled in the emergency department and postoperatively, identified a probable mortality benefit of helmet continuous positive airway pressure (CPAP) and possible benefit of HFNO and both facemask and helmet NIV compared with COT.[214] Dedicated trials of non-invasive oxygen delivery in covid-19 have identified a likely benefit of early CPAP therapy but not helmet NIV compared with COT.[215 216]

In the most severe cases of ARDS, veno-venous extracorporeal membrane oxygenation (ECMO) can be used as rescue therapy. An international RCT (EOLIA) of veno-venous ECMO for severe ARDS (PaO_2 ≤50 mm Hg for three hours, ≤80 mm Hg for six hours, or hypercarbia with acidaemia) compared with usual care found no statistical mortality benefit but was stopped early. The point estimate favoured ECMO therapy for the primary trial outcome of 60 day mortality with an upper 95% confidence bound of 1.04.[196] A subsequent systematic review and meta-analysis concluded that ECMO reduces 30 day and 60 day mortality, although the analysis is limited by the inclusion of only two RCTs.[217] Interpreting the utility of ECMO in covid-19 is difficult given the variability in practice for treating covid-19 ARDS early in the pandemic, whether because of strain on resources or because of the belief that covid-19 represented a novel ARDS phenotype. The evidence supporting the use of ECMO in covid-19 ARDS derives from observational studies and emulation trials, but as with ventilator management, the same principles guiding management of non-covid ARDS with ECMO should probably be applied to covid-19 ARDS.[218-220]

Excessive oxygen delivery is injurious to the lung in experimental models and might potentiate ventilator induced lung injury.[221 222] Clinical data on oxygen targets for patients in ICU with hypoxaemic respiratory failure do not show a consistent benefit of conservative versus liberal oxygen therapy,[199 223-225] although frank hyperoxia seems to be harmful.[226]

Effective ventilator management can be supported by several strategies that have shown benefit in patients with ARDS. Prone positioning for at least 16 hours a day in patients with a PaO_2/FiO_2 <150 mm Hg reduces mortality by 17.4% compared with supine positioning and lung protective ventilation alone.[192] Prone positioning likely has a benefit even in non-intubated patients with covid-19 for avoiding endotracheal intubation.[229] A restrictive fluid strategy with a goal of net even to negative fluid balance after initial resuscitation targets are met reduces the duration of mechanical ventilation and ICU stay in patients with non-covid ARDS,[190 191] and it is also beneficial in covid-19 ARDS.[231] Aside from "hard outcomes" such as mortality, comprehensive critical care should also prioritise the patient's experience by minimising commonly reported distressing symptoms such as thirst, pain, and anxiety.[232]

Pharmacological management

No drug therapies have consistently shown benefit in all cases of ARDS. Reversible contributors should first be identified and treated. This is especially relevant for infectious causes for which antimicrobial or other therapy can be tailored to the offending pathogen or for which therapy differs from that for other causes of ARDS.[233] An emerging area of promising clinical research is the rapidly growing ability to identify the pathogen(s) responsible for ARDS—for example, by using real time rapid metagenomics in the ICU.[233 234]

Statins

The 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) are an appealing candidate for ARDS therapy because they are inexpensive, are widely available, and act on many of the pathways that are implicated in the pathogenesis of ARDS.[241 242] Two large randomised controlled trials, one testing rosuvastatin (SAILS) and the other testing simvastatin (HARP-2), found no benefit of statin therapy on clinical outcomes in ARDS.[235 243] Simvastatin has also been tested in critically ill patients with covid-19 (not restricted to patients with ARDS, although almost all patients were receiving HFNO, NIV, or mechanical ventilation). The trial was terminated early because of low enrolment, but the results showed a high posterior probability of benefit.[236]

Corticosteroids

A major area of ongoing investigation is the use of systemic corticosteroids in ARDS. The benefit of corticosteroids in unselected patients with ARDS has been extensively studied with mixed results.

Prognosis and complications

Pulmonary dysfunction in ARDS is intimately connected with extrapulmonary organ dysfunction, especially of the brain, kidney, and heart. Extrapulmonary organ dysfunction is common in ARDS, with increasing prevalence as the severity of ARDS increases.[252] Patients with ARDS are at risk for delirium and long term cognitive impairment as a result of both ICU interventions and biological mechanisms.[253-256] Tackling delirium among patients with ARDS is an important priority, as its development is associated with long term cognitive impairment in survivors of critical illness.[257] Acute kidney injury commonly co-occurs with ARDS, complicates its management by limiting physiological tolerance for respiratory acidosis, and is associated with worse clinical outcomes,[258 259] but acute kidney injury can be under-recognised in ARDS as a result of fluid management strategies.[260] The relation between lung injury and kidney injury is complex. Experimental models have shown that lung injury increases inflammatory mediators in the kidney independent of systemic inflammation and that renal ischaemia induces pulmonary injury with impairments in fatty acid oxidation via mitochondrial damage associated molecular patterns.[261 262] Thus renal and pulmonary injury likely co-occur as a result of true organ cross-talk. Cardiac dysfunction including right ventricular dysfunction because of hypoxic vasoconstriction and global myocardial damage as a result of hypoxaemia is also an important complication of ARDS.[263]

Many studies in ARDS focus on short term outcomes such as 30 day mortality and length of stay in ICU, but critical illness is a major life event with long term implications. This has increasingly come to the forefront during the covid-19 pandemic with the widely publicised syndrome of "long covid." Before covid-19, the long term effects of ARDS were already being studied.[264] ARDS can lead to pulmonary fibrosis; pulmonary function tests indicate that mild restriction with mild-to-moderate diffusion capacity abnormalities persists at one year.[265] Extrapulmonary manifestations are also common after ARDS, with persistent exercise capacity and functional limitations and psychological sequelae in both patients and caregivers up to five years after diagnosis.[266] Interestingly, although long term functional disability is common in both covid-19 and non-covid ARDS, a study comparing survivors of covid-19 ARDS with historical controls found that these limitations are more common and more severe in patients with non-covid ARDS.[267] A better understanding of the long term consequences of ARDS, their mechanisms, and interventions to improve quality of life in survivors is an important area for future study.

Guidelines

The The American Thoracic Society (ATS) and European Society of Intensive Medicine (ESICM) have recently released separate updated practice guidelines (updated from their joint guidelines in 2017)[289] for the management of ARDS.[209 210] Both organisations recommend the use of low tidal volume ventilation (4-8 mL/kg predicted body weight), and the ATS also recommends limiting plateau pressure to 30 cm H_2O or less.[209 210] The guidelines also agree on a recommendation against the use of prolonged high PEEP recruitment manoeuvres, and ESICM suggests against brief recruitment manoeuvres as well.[209 210] Other areas of agreement are the use of prone positioning in moderate-to-severe ARDS and the use of veno-venous ECMO for severe ARDS.[209 210] ESICM also suggests awake prone positioning for non-intubated patients with covid-19 AHRF.[210]

Neither organisation explicitly endorses the expanded global definition of ARDS, rather acknowledging that the evolution of the definition of ARDS is an ongoing area of discussion, although the new global definition of ARDS included substantial global input from critical care members from 21 critical care societies.[8] The ESICM guidelines discuss PICO ("patient/population, intervention, comparison, outcome") questions "applicable to ARDS being managed with HFNO," indicating that at least some patients managed with HFNO have the same disease process as those with Berlin defined ARDS.[210] The ESICM guidelines discuss the ventilatory management of non-intubated patients with ARDS/AHRF. ESICM recommends the use of HFNO over conventional oxygen therapy to reduce the risk of intubation in this population and suggests that CPAP/NIV should be used rather than COT and can be considered instead of HFNO to reduce the rate of intubation in AHRF from covid-19. The ATS guidelines do not cover this population.[209]

Key differences between the guidelines include conditional recommendations from the ATS in favour of corticosteroids in all ARDS, a high PEEP titration strategy in moderate-to-severe ARDS, and the early use of neuromuscular blockade in severe ARDS.[209] By contrast, ESICM does not cover corticosteroid use, does not make a recommendation for or against a high PEEP titration strategy, and recommends against the routine use of neuromuscular blockade in non-covid ARDS but does not recommend for or against neuromuscular blockade in covid ARDS.[210] ESICM also recommends against extracorporeal carbon dioxide removal, which is not covered by the ATS guidelines.[209 210] The Society of Critical Care Medicine has also recently released guidance specifically on the use of corticosteroids in ARDS, pneumonia, and sepsis and suggests their use in ARDS.[239]

HOW PATIENTS WERE INVOLVED IN CREATION OF THIS ARTICLE

Eileen Rubin, who is a survivor of acute respiratory distress syndrome (ARDS), reviewed this manuscript. ER specifically drew our attention to the minimal change in therapies for ARDS since her diagnosis 30 years ago and the need for new clinical trial designs to individualise treatments. She also emphasised how covid-19 drew attention to racial disparities in medical care not only for chronic conditions but also for acute conditions such as ARDS.

Competing interests: See bmj.com.

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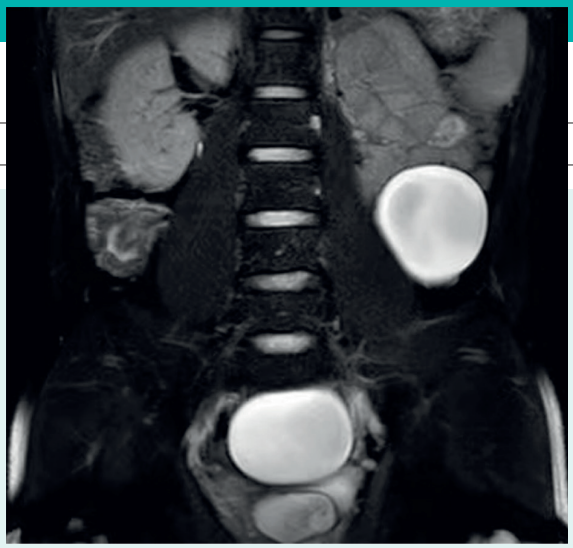
MINERVA

Renal agenesis and abdominopelvic cysts

This man in his early 20s presented with the sensation of incomplete bladder emptying. On examination, a painless lump was found in the left lower abdomen, and on digital rectal examination, there was a soft mass at the posterosuperior aspect of the left lobe of the prostate. Ultrasonography showed normal bilateral testicles, epididymides, and spermatic cords, and renal function and semen analysis were within normal limits. Left renal agenesis, ipsilateral ureteric cyst, and seminal vesicle cyst were detected on magnetic resonance imaging (figure). Zinner syndrome was diagnosed.

Zinner syndrome is a rare congenital anomaly of the urogenital tract, comprising seminal vesicle cyst, ejaculatory duct obstruction, and ipsilateral renal agenesis. The condition can be asymptomatic, or present with infertility, abdominal pain, or lower urinary tract symptoms in the second to fourth decades of life. Patients who are symptom-free can be managed conservatively, with surgical intervention recommended for symptomatic relief or associated infertility. After laparoscopic excision of seminal vesicle and ureteric cysts, the patient's symptoms improved.



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Patient consent obtained.

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Self-experimentation

Self-experimentation has a long history in medicine and physiology. In 1903, for example, the neurologist Henry Head had his radial nerve severed to investigate the tempo of recovery of sensation (https://history.rcp.ac.uk/inspiring-physicians/sir-henry-head). In the same tradition, virologist Beata Halassy recently injected herself with oncolytic viruses that she grew in her own laboratory. She was treating a recurrence of breast cancer at the site of a previous mastectomy. After two months the tumour had shrunk and could be surgically excised (*Vaccines* doi.org/10.3390/vaccines12090958).

Parental history of memory impairment

Four thousand people aged 65 to 85 without signs of cognitive impairment had their levels of cortical β-amyloid measured by positron emission tomography (*JAMA Neurol* doi:10.1001/jamaneurol.2024.1763). After adjusting for age, sex, and apolipoprotein E genotype, a parental history of early onset of memory impairment was associated with a higher burden of amyloid. A maternal history of late onset memory impairment was also associated with increased amyloid but that wasn't true for a paternal history of late memory impairment. The investigators think that this points to the involvement of genes on the X chromosome, but the history of parental memory loss wasn't verified and might have been affected by recall bias.

Thalamotomy for essential tremor

Unilateral ultrasound ablation of ventralis intermedius nucleus of the thalamus is an effective treatment for disabling essential tremor. The problem of course is persisting contralateral tremor. Until recently, bilateral lesioning was thought unacceptably risky, but a series of 51 cases treated at seven centres in the US suggests that the risks can be managed by carrying out the intervention in stages (*JAMA Neurol* doi:10.1001/jamaneurol.2024.2295). Tremor severity was reduced and functional disability scores improved, while adverse events for speech, swallowing, and ataxia were mostly mild and transient.

Vaccine scepticism

The prize for most lives saved by public health interventions surely goes to the provision of clean water. Vaccination against common infections comes a close second. So the nomination of a vaccine sceptic as secretary of health in the US President elect administration seems inexplicable. An article in *The Spectator* argues that the public's loss of faith in vaccination is an inevitable consequence of official misinformation about the efficacy and safety of covid-19 vaccines during the pandemic (https://www.spectator.co.uk/article/the-experts-who-enabled-rfk-jrs-rise/).

Covid-19 and adverse cardiac events

On the subject of covid-19, data from the UK Biobank show that infection with SARS-CoV-2 roughly doubles the subsequent risk of major adverse cardiac events (*Arterioscler Thromb Vasc Biol* doi:10.1161/ATVBAHA.124.321001). The increase in risk is present at all levels of severity of covid-19, from being asymptomatic but with a positive polymerase chain reaction test, to needing hospitalisation, although the increase in risk is greater after more severe infection. The increased risk persists for at least three years after the infection.

Simultaneous administration of covid-19 and influenza vaccines

Side effects aren't commoner when covid-19 and influenza vaccines are given simultaneously than when they are given separately. Three hundred people were randomised either to receive an mRNA covid-19 vaccine plus a quadrivalent inactivated influenza vaccine and then a placebo injection one to two weeks later, or to receive a covid-19 vaccine plus a placebo injection with the influenza vaccine delayed for one to two weeks. Adverse reactions were reported by around a quarter of participants but were no more likely in those getting both vaccines together (*JAMA Network Open* doi:10.1001/jamanetworkopen.2024.43166).

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