DRUG SAFETY

New Network to Track Drugs and Vaccines in Pregnancy

Pregnant women worry about—and avoid—exposure to virtually everything that might be risky, from tap water to soft cheeses. Many also jettison drugs they need, for fear of harming their baby.

Unfortunately, existing data are fuzzy about the dangers of using—or going without—key medications. "We can tell you what happens in a rat or a rabbit," says Christina Chambers, an epidemiologist at the University of California, San Diego. But a pregnant woman? For most medications, "we are flying by the seat of our pants," says Chambers, a situation she calls "appalling and frustrating." As a result, both doctors and patients are jittery about whether to continue or drop potentially risky treatments during pregnancy.

Playing it safe. Flu vaccines top the list of therapies to be studied in pregnancy.

A new effort to bring risks into focus is being launched this week with $12.5 million from two U.S. agencies. It will start by examining asthma medications called short-acting beta agonists, as well as flu vaccines and antivirals for influenza. Called VAMPSS (the Vaccines and Medications in Pregnancy Surveillance System), the program will be funded for 5 years by the Agency for Healthcare Research and Quality and for 2 years by the Biomedical Advanced Research and Development Authority and coordinated by the American Academy of Allergy, Asthma, and Immunology. An advisory committee that includes members from pediatric and obstetric groups and the Centers for Disease Control and Prevention will guide VAMPSS's research.

This push for data began 8 years ago. Chambers and two of her colleagues—asthma specialist Michael Schatz of the Kaiser Permanente Medical Center in San Diego, California, and Allen Mitchell, who directs the Slone Epidemiology Center at Boston University—had spent years researching the issue. But their studies were hampered by too few volunteers and potentially imprecise data from mothers asked to remember every pill they'd taken.

The new program aims to get more robust results by bringing together two long-standing efforts. The first, led by Mitchell, has collected information over the years on 37,000 babies, most of them with congenital malformations, and their mothers. Mitchell plans to recruit at least 2000 more babies in each of the next 2 years for VAMPSS.

Chambers, meanwhile, is one of the leaders of the Organization of Teratology Information Specialists (OTIS). It counsels between 70,000 and 100,000 pregnant women and health-care providers each year in the United States and Canada about drug and other exposures in pregnancy and lactation. It also invites some callers to enroll in research studies in which they and their babies are followed over time. OTIS will recruit thousands of these women for the VAMPSS studies on asthma and flu treatments and flu vaccines.

OTIS takes an approach that improves the quality of the data: It works with women before their babies are born. But its cohorts are often too small to link a specific medication with a specific birth defect. On the flip side, the project headed by Mitchell has the statistical power to focus on one birth defect at a time, but it relies on mothers to recall exposures during pregnancy. By conducting studies in sync on the same treatment or vaccine, there's "no question" that VAMPSS will be superior to existing efforts and far more systematic, says Gideon Koren, who directs the Motherisk Program at the Hospital for Sick Children in Toronto, Canada, which is part of OTIS's North American network.

The government support helps fill a serious gap. "It's not a secret that most drug companies … don't want anything to do with pregnancy," says Koren. Drug companies so far have declined to help fund VAMPSS. To survive long-term and branch out to other drugs and vaccines, as its leaders hope it will, it needs industry money.

VAMPSS is coming together now partly because of the H1N1 flu. H1N1 was "a situation that seemed to be uniquely affecting pregnant women" who were at high risk for complications if they contracted it, says Schatz, a past president of the allergy academy. Meanwhile, the U.S. Food and Drug Administration (FDA) is asking companies to focus more on drug safety in pregnancy after a drug is approved. In December, FDA announced it was setting up the Medication Exposure in Pregnancy Risk Evaluation Program, which relies on insurance company databases to look for signals.

VAMPSS is focused as much on demonstrating safety as on finding hazards. "In some ways there's more benefit" to showing safety than risk, says Chambers, because women and their babies can be harmed by a poorly controlled disease. Studies of pregnant women with asthma have found that those who have asthma attacks are more likely to give birth to babies with low birth weight and, in one study, with birth defects.

But just how reassuring can any study be?

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"It's been really difficult" to prove that drugs or vaccines are safe in pregnancy, says Allison McGeer, an infectious disease specialist at Mount Sinai Hospital in Toronto, who is studying flu vaccines in pregnancy. Although McGeer believes flu vaccines are safe, she hesitates to prescribe antiviral drugs to pregnant women who are mildly ill or as a preventive treatment. "Those of us who don't deal routinely with pregnant women are very afraid to do anything," she says.

One area not addressed by VAMPSS and most other studies is whether medications taken during pregnancy can cause effects in children years later, such as learning difficulties in school. "We need to focus more on the long-term effects," says Lars Pedersen, an epidemiologist and obstetrician at Aarhus University in Denmark, who has studied antidepressants and other drugs in pregnancy. But that is not easy to do.

It's not so much that "drugs are out there causing problems," says Schatz, although some probably are. The bigger challenge, he believes, is the uncertainty: Which drugs are dangerous to a fetus, and which are not?

–JENNIFER COUZIN-FRANKEL

PHYSICS

Century-Long Debate Over Momentum of Light Resolved?

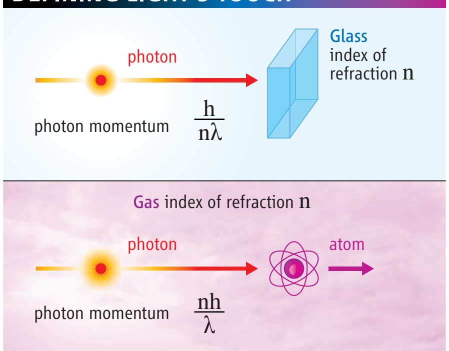
What is the formula for the momentum of light zipping through a transparent material? That may sound like a question on a high-school physics quiz, but physicists have been debating the matter ever since two different formulas were proposed more than 100 years ago. Now Stephen Barnett, a theorist at the University of Strathclyde in Glasgow, U.K., says he has resolved the famed "Abraham-Minkowski dilemma." Both formulas are correct, he says, but they denote different things and apply in different contexts.

Others had suggested that each formula might be correct in its own way, but Barnett spells out precisely when each is relevant, says Robert Boyd of the University of Rochester in New York state. "Steve tells you how to apply them correctly," Boyd says. "I think [the work] has a good chance of being definitive."

Everyone agrees that the momentum of a photon zinging through empty space is given by a fundamental constant divided by the light's wavelength. When the light enters a medium such as glass or a gas, however, it slows down, which is why a lens bends light. What then happens to the light's momentum? Key to this question is the material's "index of refraction," the ratio of light's speed in a vacuum to its speed in the material, a number typically larger than one. In 1908, German mathematician Hermann Minkowski argued that the momentum of light in a material equals its momentum in the vacuum multiplied by the index of refraction, making it greater than the vacuum momentum. A year later, his compatriot, physicist Max Abraham, argued that the momentum of light in a material equals the vacuum momentum *divided* by the index, making it smaller than the vacuum momentum.

Thought experiments and real-world data can be found to support each formula. For example, imagine a photon speeding toward a block of glass (see diagram). Together, the glass and the photon possess a total mass and energy that flows in the same direction as the photon. According to Newton's laws of motion, that flow should continue unabated as the photon passes through the glass. But within the glass, the photon slows down. So to maintain constant energy flow, the glass has to recoil in the same direction. From this premise, a little algebra leads to Abraham's formula for the photon's momentum in the glass.

DEFINING LIGHT'S TOUCH



Riddle me this. Incompatible equations for a photon's momentum have long puzzled physicists.

On the other hand, imagine firing a photon at an atom in a gas. Suppose the atom can absorb light of a wavelength slightly longer than that of the approaching photon. Then to soak up the photon, the atom must speed away from the light source so that from its perspective the light wavelength stretches—just as a siren's pitch dips if you're in a car rushing away from the siren. The size of that "Doppler shift" is proportional to the gas's index of refraction. Starting from that premise, a little math yields Minkowski's formula.

Actually, Barnett argues in the 19 February issue of *Physical Review Letters*, the two cases describe different kinds of momentum. Abraham's formula gives the "kinetic momentum"—essentially the mechanical punch the photon packs as it hits the glass. Any experiment to measure such a punch will agree with Abraham's formula. Minkowski's formula gives the subtler "canonical momentum"—which, loosely speaking, is tied to the wave nature of light and is higher in a material than in vacuum because the light's wavelength is shorter in the material. Any experiment to probe wave effects will jibe with Minkowski's formula.

More technically, the canonical momentum is a mathematical quantity connected to movements in space. A theorist can write down a quantum "wave function" describing an atom sitting in an electromagnetic field. To move the atom to another spot, the theorist must change the wave function by performing a specific mathematical operation that involves the canonical momentum. That's why in the thought experiment with the moving atom, it's the canonical momentum that counts.

Given the debate's long history, few expect the work to win immediate acceptance. "Various people have taken rather strong views, you might say verging on religious beliefs," says Paul Lett, a physicist at the U.S. National Institute of Standards and Technology in Gaithersburg, Maryland. Barnett says he's game to take on the naysayers, however: "If somebody exposes some flaw, then I suppose I shall have to—Oh, they won't!"

–ADRIAN CHO

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