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The polypill and medicines access: two decades and counting

The polypill has finally been approved for the WHO's Essential Medicines list, but hurdles remain in terms of access and availability, write Anthony Rodgers and Richard Smith

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There have been two landmarks in 2023 for the polypill: one momentous, the other sobering. The momentous event is the inclusion—after several attempts—of polypills for high risk primary and secondary prevention of cardiovascular disease in the World Health Organization (WHO) List of Essential Medicines.[1] This is important as more than 90% of people in the world with cardiovascular disease still don't receive the antiplatelet, statin, and blood pressure lowering medicines that evidence showed to be effective over 30 years ago.[2] Availability and affordability are particular challenges in low and middle income countries, where most people with cardiovascular disease live.[2 3] Cardiovascular disease caused 393 million lost healthy life years in 2019—15% of total global disease burden—compared with 312 million (12% of total) 20 years earlier.[4] Most premature deaths can be prevented with access to essential cardiovascular medicines.[5]

The second landmark is the 20 year anniversary of the seminal "polypill papers" in *The BMJ*, which brought the concept to widespread attention.[6-8] In an edition hailed by one of the authors (RS) "as the most important for 50 years," not only was use recommended for people with vascular disease, but also for all people aged over 55, with the aim of more than halving cardiovascular events. It is even longer since the WHO Wellcome meeting indicated it "could take five years or more" to develop an aspirin, statin, blood pressure combination to help improve essential medicine access.[9] Unfortunately, clinical trials took much longer than expected to complete because research grants for the trials were slow to appear, small, and uncoordinated between countries. Nevertheless, the evidence largely supports the estimates made in the original papers in terms of benefits of joint treatment with aspirin, statin, and blood pressure lowering [10 11] and shows the polypill to be more effective than "usual treatment."[10] Side effects are consistent with those expected from the component medicines and comfortably exceeded by benefits in patients at high risk.[10]

The main reason that the polypill is still not widely available is market failure. Current sets of market incentives encourage industry to take high risk bets of hundreds of millions, if not billions of dollars to launch new chemical entities, which are inevitably expensive and strain the budgets of health systems. But there is little incentive for companies to make lower risk investments of tens of millions of dollars to develop established medicines, even when potential benefits to public health are huge.[12] This remains a major issue in many therapeutic areas. Market failure for neglected tropical diseases is a familiar problem, and the situation with the polypill shows it exists for non-communicable diseases as well.

The polypill has also exposed a fault line in medicine, both in practice and regulation: where the perfect is the enemy of the possible. Prescribing experts have criticised polypills, holding tightly to the concept that there is an optimal set of drugs and doses for every person, that can be reliably determined and implemented. In practice most patients miss out entirely drugs in one or more recommended classes in the long term. Regulators have been similarly impractical: still the only option for approval in Europe is "substitution" for people already taking all component drugs at the same doses. This defines a set of people both small in number and with little unmet need.

Despite these challenges, some polypills have finally been developed and launched. Several were launched in India, and thanks largely to the public-private partnership with Centro Nacional de Investigaciones Cardiovasculares and Ferrer, a polypill containing ramipril, atorvastatin, and aspirin has been launched in 26 countries worldwide.[10] An application to include fixed dose combinations in the WHO Model List of Essential Medicines for high risk primary and secondary prevention of atherosclerotic cardiovascular diseases in adults summarises the evidence that supports the effectiveness and safety of the polypill.[10] Yet the goal of providing easily available, affordable polypills in low and middle income countries is still far off, although inclusion in the WHO List of Essential Medicines could make a big difference.

More broadly, the polypill story provides lessons on how we prioritise and fund the development of affordable innovations. We recommend reframing incentives for private enterprise to make acceptable financial returns on innovations of public health importance without needing to develop new chemical entities. Public funding and public-private co-funding should be increased for translational research on better uses of existing medicines, particularly those with the largest public health benefits. Regulatory frameworks can be reformed to reduce unnecessary hurdles for repurposed medicines. This would help make these treatments more affordable and available. Finally, we must adopt a more patient-centred approach to drug development and reimbursement. Patients ultimately pay for most medicines' development directly or indirectly and should have a greater say in research priorities. We predict this would include much faster development of patient-oriented products such as the polypill.

With the burden of disease and the cost of health systems both rising, we urgently need these reforms. We shouldn't have to wait another 20 years for the wider availability of the polypill and other low-cost but highly effective innovations.

Competing interests: Anthony Rodgers wrote the editorial "A cure for cardiovascular disease?" accompanying the 2003 BMJ polypill papers and has tried and failed several times over 20 years to bring a polypill to the market. He is employed by The George Institute for Global Health (TGI) and Imperial College London, and seconded part time to George Medicines Pty Ltd (GM), which is partly owned by George Health Enterprises (GHE), the social enterprise arm of TGI. TGI holds patents for ultra-low-dose fixed-dose combination products for the treatment of hypertension and diabetes, and Anthony Rodgers is listed as one of the inventors (US 10 369 15; US 10 799 487; US 10 322 117; US 11 033 544). GHE and GM have received funding from public and private investors to conduct the research required for regulatory approval of cardiovascular combination products. Professor Rodgers does not have a financial interest in these patent applications or investments.

Richard Smith was the editor of the *BMJ* when it published the "polypill papers," and he remains an advocate for the use of polypills. He was a subject in a cross over trial of the polypill, and he has taken a polypill every night for about 15 years, since he was 56. He has no symptoms or signs of cardiovascular disease and has experienced no side effects. He pays for the polypills and receives them through the post as part of the Polypill Prevention Programme. His GP knows that he takes the polypill, but he has never consulted his GP about blood pressure or vascular disease. He has no financial interest in the polypill beyond having to buy it for himself.

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