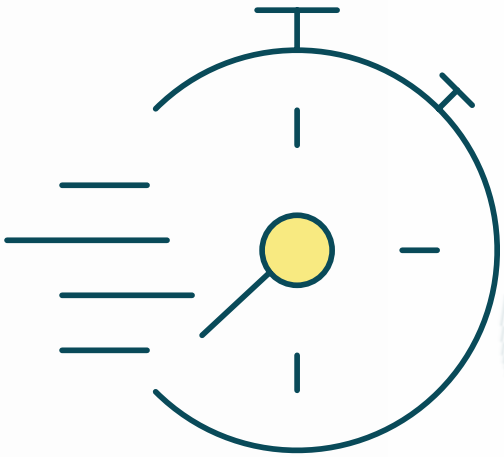
# A BLUEPRINT TO VACCINATE THE WORLD

GreenLight BIOSCIENCES™

*Every month we shorten the pandemic is worth:*

## $500 billion



To a citizen of a rich country, it may feel that the Covid vaccination program is going fast. By summer, it's reasonable to expect that more than 75% of the adult population of the USA and UK will have had a first dose of the vaccine. The EU, Japan and other developed nations will be not far behind; most likely they will reach that milestone in the autumn.

But this is not fast enough. Billions of people will still be left unprotected, mainly in the developing world. India and China have made impressive strides, but it is unlikely that the whole world will have been vaccinated until the end of 2022 – and even that is optimistic.

This is too slow; much too slow. We need to speed the process up, enormously. The costs and the risks are too great.

There is an obvious humanitarian cost. Already, more than 2 million people are dead, with more dying each hour; on top of that, there have been at least 100 million confirmed cases, many of them causing severe, lasting illness.

This is worsened by economic damage. The International Monetary Fund estimates that the cost of the pandemic is $28 trillion. Even medium-sized economies, such as Britain or France, are losing more than $1bn every day that it continues. Nobel-prize winner Michael Kremer estimates that every month that we shorten the pandemic is worth $500bn. It is worth spending billions of dollars just to speed up our recovery by a single day.

Most alarmingly of all, as long as the virus is still out there, it is still mutating. We have warned for months of this threat, and it is now obvious that the virus is getting better at evading vaccines. Every extra infection is a risk; the billions more infections we will likely see over the next two years are a huge gamble.

**The only way to solve this is to accelerate our plan to vaccinate the world.**

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# HOW DO WE VACCINATE THE WORLD?

## We have to do two things:

1. Make vaccines for every person in the world – around 15 - 20 billion doses with wastage – and distribute them.

2. Do that before a serious mutation makes vaccines significantly less effective.

If we're not fast enough to prevent major mutations, we'll need to vaccinate the world all over again to tackle new strains, which will mean rapidly making and distributing billions of doses again. Even if we do prevent major mutations, we need to be ready with billions of doses because if immunity fades after a year or two, we'll need to continue vaccinating.

### ABOUT GREENLIGHT BIOSCIENCES

Having started by applying RNA technology to large scale crop protection, GreenLight Biosciences developed an innovative manufacturing process that is integrated, simple, scalable and eliminates critical supply chain dependencies.

Even before the pandemic, we began focusing these unique manufacturing capabilities on pharmaceutical-grade messenger RNA production for vaccines and treatments, including gene editing for Sickle Cell Disease in partnership with the Bill & Melinda Gates Foundation.

One of the small coterie of early RNA-focused biotech startups, GreenLight Biosciences was founded in 2008 and has a broad portfolio of products under development and regulatory review. Described by Business Insider as a biotech VCs are watching, the company has raised $250m to date, including a 100m+ round last year to accelerate efforts around a COVID-19 vaccine candidates and mRNA manufacturing.

Our initiatives include finding ways to support biodiversity, protect bees and other pollinators, treat rare diseases such as Sickle Cell Disease as well as develop vaccines for seasonal flu and the current COVID-19 pandemic.

Our advisory board includes Professor Drew Weissman, RNA pioneer, Mark Dybul, global public health expert, and Luc Debruyne, former President of GSK vaccines. Key life sciences investors include Morningside, Baird Capital, and Cormorant Asset Management.

Andrey Zarur, GreenLight's CEO and founder, is a leading public voice on the pandemic and RNA vaccines, having written opinion articles for Fortune and Stat and quoted frequently in major media, including the Financial Times, Investors Business Daily, Wired, Business Insider and CNBC.

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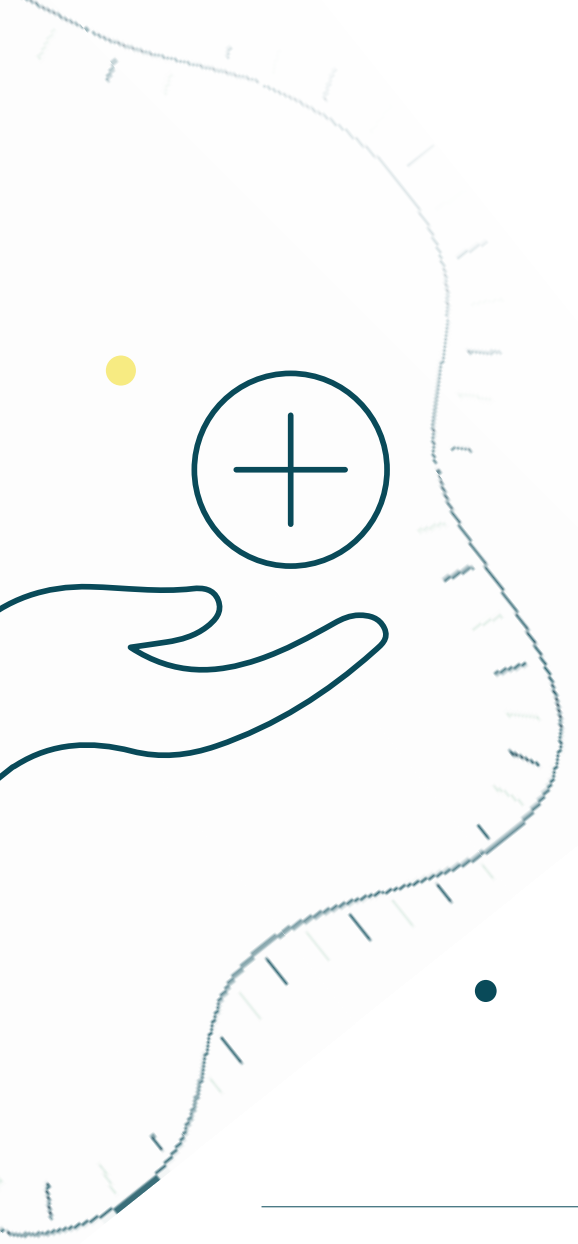

**An annual program to vaccinate billions is possible:**

We do it already with the flu. Just as with flu, we need to be ready to develop new vaccines every year, and distribute enough to vaccinate the world. It will need a larger-scale program – we give about 1.5 billion people the flu vaccine per year; this would be several times more – but it's possible to do that.

Scaling up vaccination capacity will have knock-on benefits: it will give us the infrastructure to tackle future pandemics, as well as this one. Future pandemics, especially flu pandemics, are a much bigger threat. While seasonal flu is generally milder than Covid, new strains might not be, and flu mutates much faster, making it harder to contain. Extra weapons to fight flu would be of huge value.

## So how do we actually make enough vaccine?

**We need to address three major roadblocks:**

1. **Vaccine Manufacturing Capacity**

2. **Supply Chains**

3. **Next Generation Vaccines**

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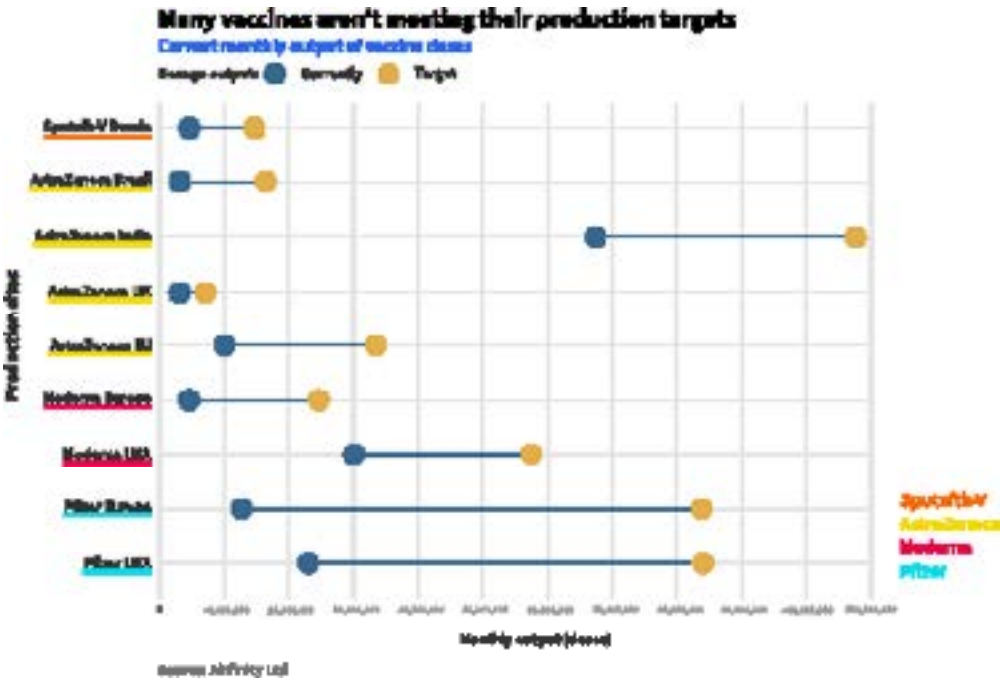
# 1. VACCINE MANUFACTURING CAPACITY:

## The challenge

Producing enough vaccine, quickly enough, is an underappreciated challenge. Even if every manufacturer delivered on their projections, most calculations predict that it will take two years to vaccinate the planet.

Unfortunately, this may be too optimistic. Industry analysts Airfinity suggest that many vaccine factories are running well behind schedule.

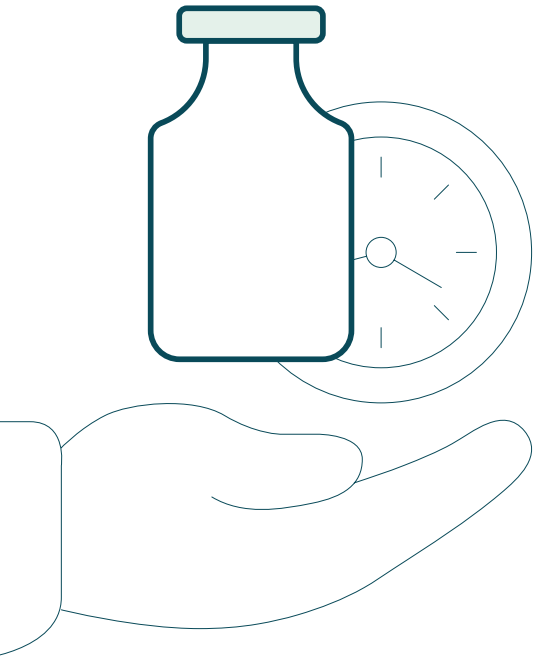
There's a further challenge: the risk of vaccine nationalism. It will be hard to get countries to share their vaccines equitably with other countries that have less, so the ideal vaccine strategy has to include vaccine production sites distributed around the world.




The graph shows the current monthly production of different vaccines from their respective production locations, with the target monthly output capacity. Currently, none of the approved vaccines are meeting their targets, with some facilities struggling more than others, impacting the countries expecting deliveries.

# The solution

Right now, there are only four messenger RNA vaccine factories in the world, all of them in either the USA or the European Union.[1] Others are being built, but on the current trajectory that number may only double by the end of 2021. To defeat Covid, we need a dramatic global expansion of messenger RNA capacity.



**We propose a network of seven RNA vaccine factories capable of vaccinating the entire human population quickly. They would be created by building, or converting,[2] pharma-grade manufacturing plants. These factories should be distributed across the world so that most of the world's population lives within a few days' travel of at least one.**

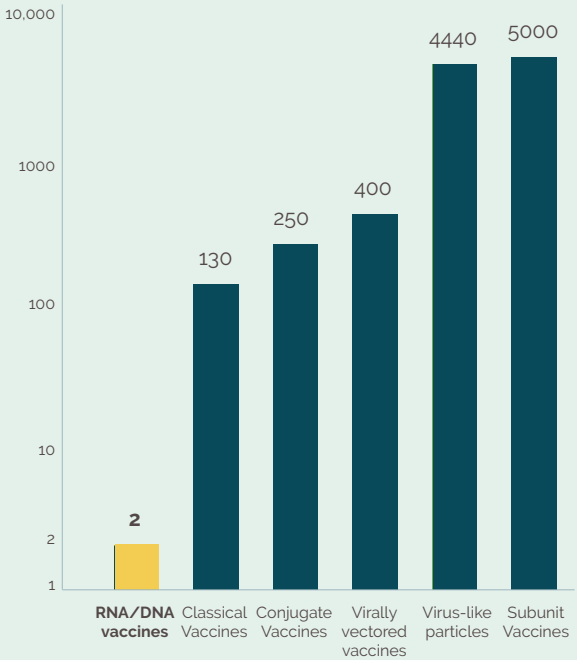
### WHY RNA VACCINES?

RNA vaccines scale easily. It takes just 1/200th as much bioreactor space to make a million doses of an mRNA vaccine as it does an adenovirus vaccine. This means that a small network of factories can supply the whole planet.

The process of scaling is also simpler than other vaccines. Unlike other vaccines, RNA is not grown in cells. This means that many of the challenges faced by other manufacturers do not arise.

RNA vaccines are faster to adapt than any other vaccine - meaning that we can move from identifying a new variant to testing it in a few weeks, and deploying soon afterwards. Adenovirus vaccines are almost as fast, but other types of vaccines are much slower. So in reality RNA is the best bet (although as the CEO of an RNA company, I suppose I would say that).

Bioreactor volume needed per 1 million vaccine doses




Source: Branton, Liddell, Rosamonte, Taylor, Lucas, Humphreys in The Chemical Engineer, April 2020

**A global vaccine network would bring several advantages:**

- **Greater volume.**
- **Reduced risk should anything happen to one site; fewer eggs in one basket.** In recent months, major vaccine sites have been threatened by fire and floods. The world almost lost millions of doses of vaccine, which we could ill afford. The more factories there are, the more resilient we are to the loss of one.
- **Interchangeable inputs** – if any factory has a problem sourcing or making a vaccine component (for instance, the nucleotides that make up the active mRNA ingredient), then they can be sourced from another site.
- **Reduced incentives for vaccine nationalism.** By creating a worldwide network we both reduce the national pressure on vaccine deliveries, and encourage countries to understand that their deliveries rely on a free flow of trade.[3]

These plants would be built to be interchangeable, and would make most of their own raw materials, only importing the most specialised ingredients.

At GreenLight we can already manufacture many of the key ingredients for an RNA vaccine from yeast, sugar and water. We, and other biologics companies should be able to make a replicable process for virtually all ingredients in the next few months.

Compared to most vaccine factories, these are cheap: We estimate $200 million each. The world loses that much money to the pandemic in less than an hour, so the costs are negligible. We think they should be built within existing pharmaceutical production facilities which carry out microbial fermentation; there are many such sites in the developing world. With a priority focus it would likely take nine to twelve months to build a facility capable of producing enough doses for 1 billion people a year.

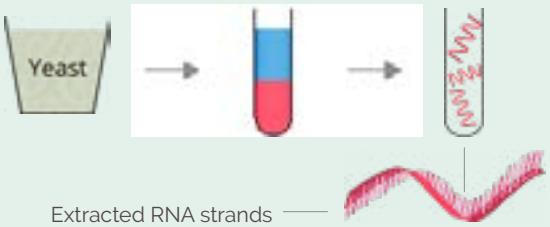
**$200MM**

*Cost of 1 RNA factory and also the equivalent hourly cost of pandemic*

## HOW TO MAKE AN RNA VACCINE

### EXTRACT

RNA can be extracted from yeast.




### BREAK DOWN

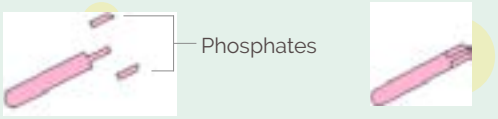
The RNA strands are broken down into **nucleotide bases** by an RNase enzyme.


### PREPARE

Free nucleotides are not ready to be reassembled into new mRNA strands until they are **energized.**

### ENERGIZE

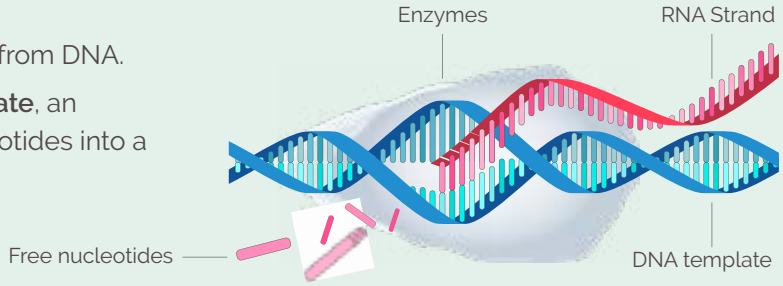
With addition of **polyphosphates**, nucleotides are converted from **monophosphates** to **energized triphosphates** ready for re-assembly.




### TRANSCRIBE

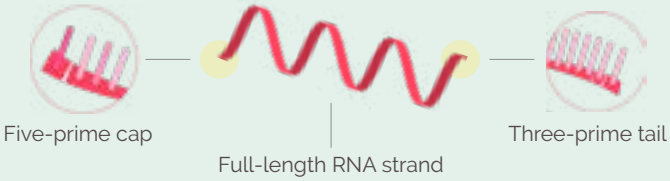
Each strand of RNA is copied from DNA.

Moving along the **DNA template**, an **enzyme** assembles the nucleotides into a **strand of RNA**.



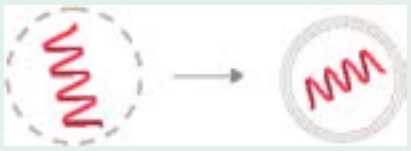

### SECURE

The strand is secured with **a cap and a tail**.




### PROTECT

The completed mRNA molecule is coated in an oily layer of **lipid nanoparticles** to protect the strand and allow entry into the cell.



### DELIVER

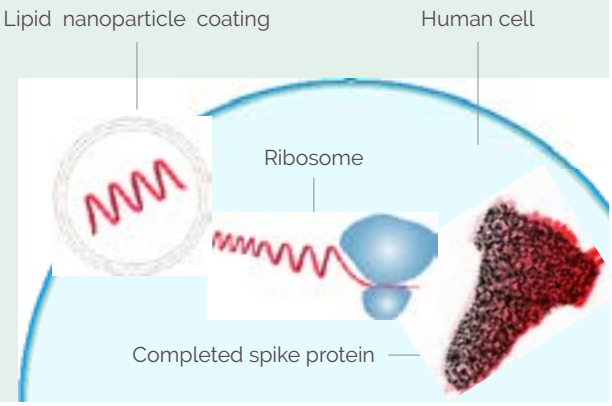
Lipid nanoparticles help deliver the strand safely through the cell membrane.

### DECODE

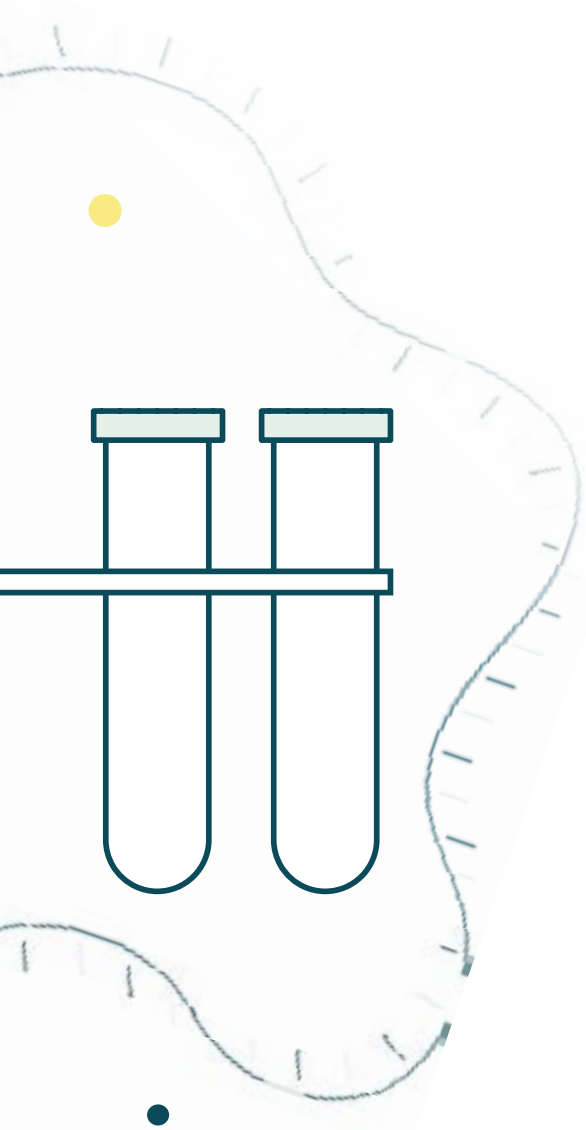
Once safely inside the cell, the ribosome translates the mRNA...

### ASSEMBLE

... to assemble amino acids into the protein specified by the mRNA, in this case a Covid spike protein.



# 2. SUPPLY CHAINS:



## The challenge

One year ago, messenger RNA was produced only in labs. Since then we have been moving to make billions of doses of vaccine. So it's not surprising that supply-chain challenges already seem to be causing delays in vaccine production.

**That has created a challenge sourcing enough ingredients, in particular:**

- DNA templates
- Enzymes that assemble the RNA strand
- Pharma-grade nucleotides, the building blocks of RNA
- Capping agents, which stop RNA degradation by the human body, and make the RNA more effective
- Lipid nanoparticles (LNPs), the packaging that delivers the RNA into your cells
- Fill and finish is backlogged

**Of those six, the three challenges we see are supplies of nucleotides, lipid nanoparticles and capping agents. Suppliers of all these ingredients are trying to scale up their production quickly, far beyond what they previously made.**

Nucleotides are widely made for food, but there are very few producers (e.g. Roche) who make them to pharmaceutical grade. At GreenLight we make our own, using yeast as the main ingredient.

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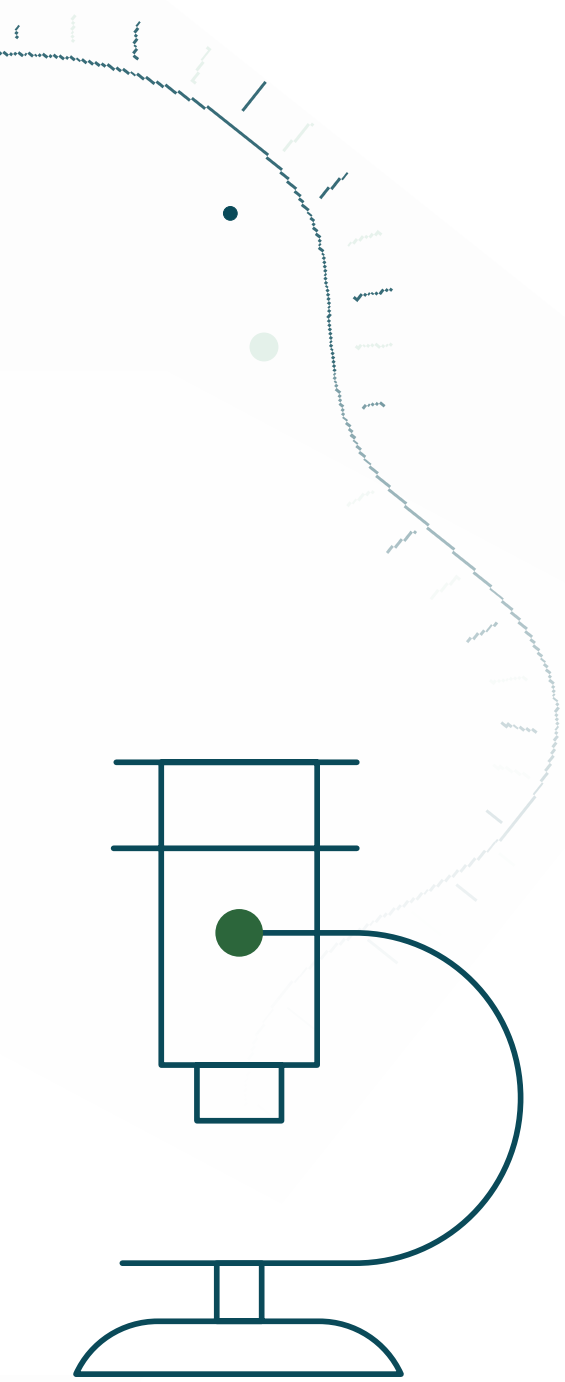
**1**

*Number of Chemical Capping Agent Suppliers Globally*

There are relatively few LNP producers – for instance, we believe there are only two in Europe. This has already led to difficulties. The Wall Street Journal has reported that 'Pfizer and its partners incurred a three-week delay securing enough raw materials to make the lipid nanoparticle'.

Finally, capping agents. There are very few capping agent suppliers – in fact for chemical capping there is only one supplier, Trilink. There are a few more for enzyme caps.

Crucially, the supply of the different ingredients are not independent problems. For instance, better LNPs can mean that less mRNA is needed for the vaccine; so if we can reduce the quantity of nucleotides needed if we improve our choice of LNP, or, conversely, if we can produce RNA more easily, we will be less constrained in our choice of LNP supply.



## The solution

In the short term, we believe industry cooperation can reduce many supply chain challenges:

1. Some companies may have already solved these problems in-house. For instance, GreenLight Biosciences can make its own pharma-grade nucleotides.
2. Suppliers can more easily scale up when they have a predictable demand. Knowing that they need to supply the ingredients for 15 billion doses, not 2 billion, as currently planned, will allow suppliers to plan.
3. Supplies can more easily be moved to where they are needed.

**Our prediction, going from our experience and the experience of our friends in the industry[4], is that many of the supply chain challenges can be fixed with a year of collaboration.**

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# Pandemic Vaccine Unit: Startup Phase

Built on a public-private partnership to achieve regional self-sufficiency

**Cost:**
Approx $200m per manufacturing unit capable of 1bn doses annually.

**Public-Private Partnership:**
Working in close collaboration with local regulatory and health authorities as well as operators on many elements.

**Startup time:**
Six months to install modular suites, plus certification time (subject to regulators).

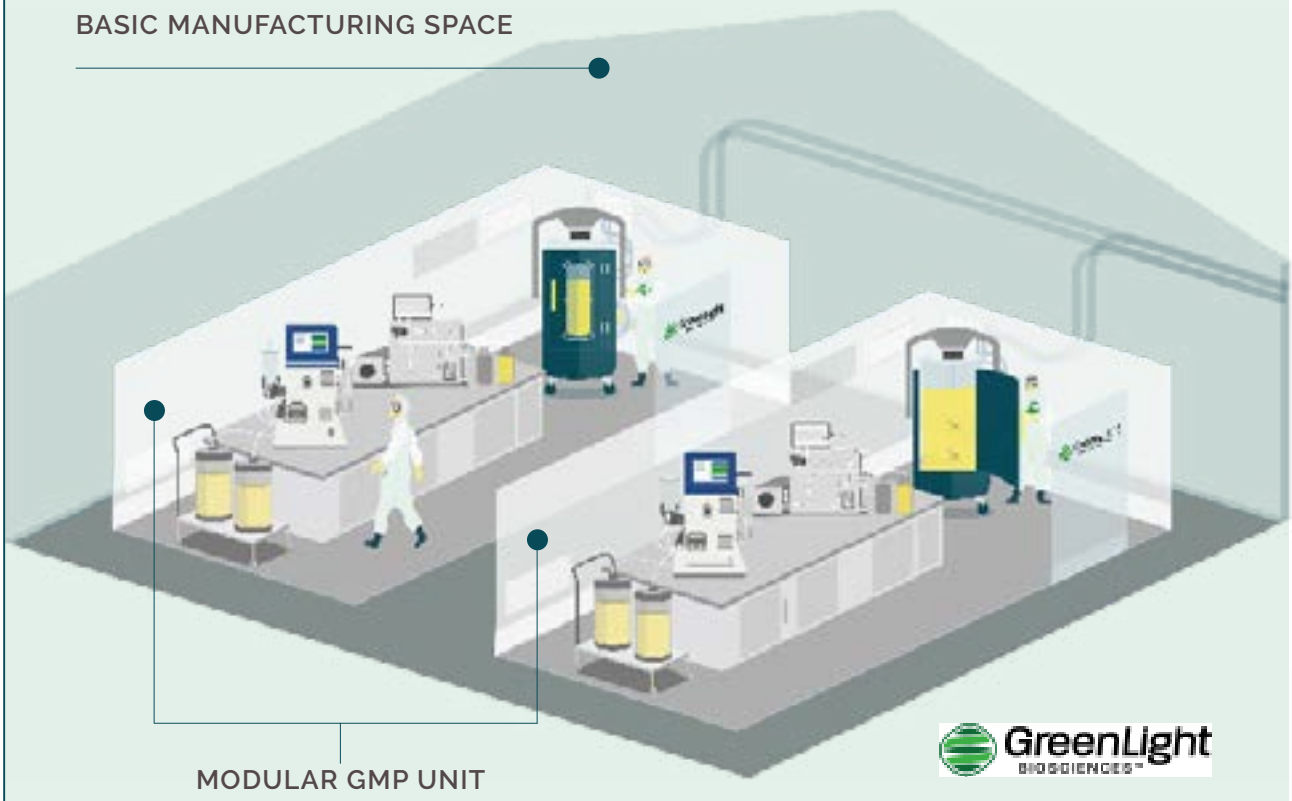
**Locations:**
To accelerate production, modular suites can be installed in existing manufacturing facilities.

**Staff:**
100 local staff for production supported by GreenLight tech transfer team with additional workforce supporting supply chain and distribution.

**Any mRNA vaccine or therapy:**
Produce any mRNA vaccine (e.g. BioNTech, Moderna, GreenLight, etc), then in non-pandemic times relevant mRNA therapies (Sickle Cell Disease, etc).

**MODULAR UNITS SET UP WITHIN EXISTING FACILITIES**

Each modular GMP unit produces roughly 17mn vaccine doses per month

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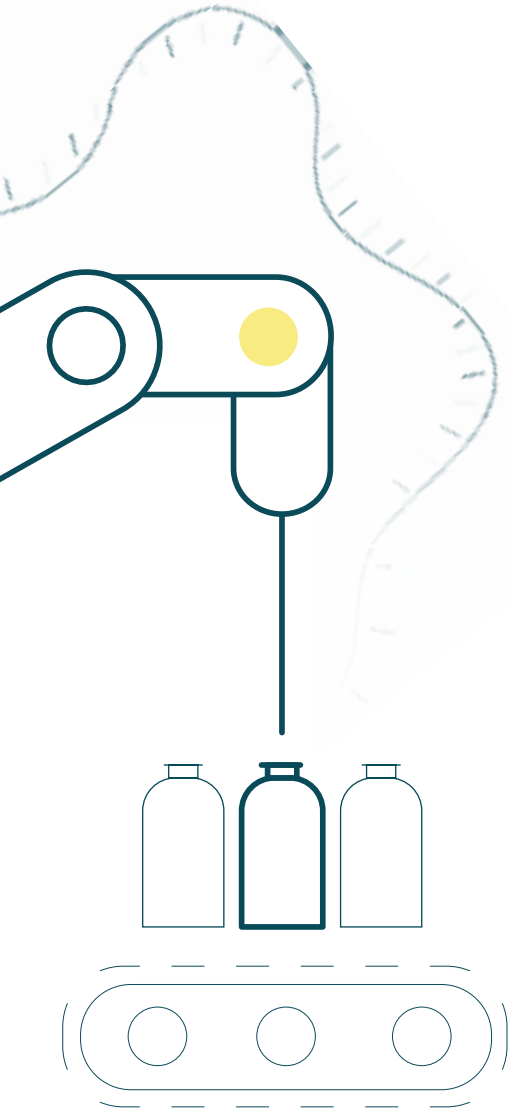
# 3. NEXT GENERATION VACCINES



## The challenge

Innovation by the RNA industry has been very impressive. But we need to keep on innovating, to solve two big challenges.

First, we need to adapt our vaccines to keep ahead of the virus as it mutates. All vaccine developers, including GreenLight, are adapting their vaccines to new variants. Luckily messenger RNA, as a platform technology, is quickly adapted.

Secondly, the first generation of RNA vaccines has technical challenges which make it harder to provide in adequate quantities. Those challenges are cold-chain distribution, a two-dose regime, and high prices.

## The solution

We need to keep improving and adapting our vaccines to deal with these challenges.

Countries with weak health infrastructures need single-shot vaccines with greater thermal and physical stability.

A single-shot vaccine will make compliance more effective. The USA struggles to get compliance with multi-dose vaccines. One review of multi-dose vaccine programs found that as little as 40% of patients completed them. This problem will be even worse in countries with weaker health systems – which are often the places that struggle most to control Covid, as we have tragically seen in Brazil.

**Injected vaccines are also a barrier; ultimately, a nasal vaccine might be the ideal solution.**

40%

*Only 40% of patients completed some multi-dose vaccine courses*

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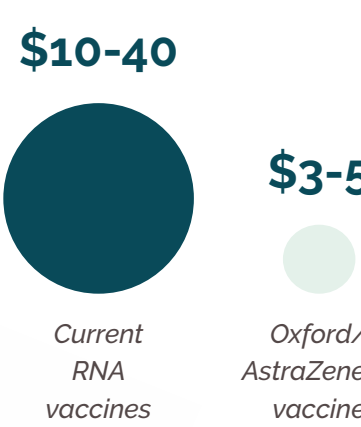



We need to develop a vaccine that can be delivered at regular refrigeration temperature. While RNA vaccines so far have had to be stored at minus 20 degrees, this is not inherent to the technology. For instance Curevac's vaccine, currently in stage III trials, keeps in a fridge for up to three months.

Finally, costs must come down. RNA vaccines, at $10-40 per dose, are significantly more expensive than the cheapest alternative vaccines, currently the Oxford/AstraZeneca at around $3-5 per dose. Again this is solvable: scaling up production and improving technology, including easing the cold-chain issue, should naturally bring prices down. Our projections are that the RNA industry should be competitive with other types of vaccines within the year.

**ADAPTING VACCINES**

To adapt a vaccine, three major areas need to be tackled.

First, vaccine developers must choose which parts of the virus to target, a process now speeded up by new computer technologies.

Secondly, samples of this new RNA have to be produced – this is made easier by increased manufacturing capacity – and tested in the lab.

Finally, human trials have to be undertaken.

Each of these is faster when adapting a vaccine than when producing a new one: we estimate that the 10 months to produce the first vaccines in 2020 can be cut to less than 5 months when vaccines are adapted.

CEPI have recently set a target of 100 days from discovering a virus to submitting a vaccine for regulatory approval. We don't believe it will be long until this is possible.

1. This excludes Curevac (Stage III trials) manufacturing and new plants being brought on stream by Moderna and Pfizer/BioNTech, such as their access to GSK/Sanofi plants. On a broader definition we expect no more than 10 global RNA manufacturing facilities by end 2020 unless action is taken.

2. Existing pharma facilities, such as antibiotics producing facilities, can be converted, with appropriate regulatory approval and testing. Some of these are currently lying idle as manufacturing has moved locations. In the case of 'concrete and steel in the ground' it would take 6-9 months from identifying a site to being ready. For an example of the concentrated distribution locations of pharma sites see: https://www.contractpharma.com/contents/view_blog/2018-02-02/an-interactive-global-map-of-pharma-manufacturing-sites/

3. Our analysis is that, outside the USA, no single country has the right manufacturing capacity to currently make RNA vaccines without imports.

4. The RNA industry is still relatively small, so while this paper comes from GreenLight Biosciences we are confident that most of our colleagues in the industry will agree with it.

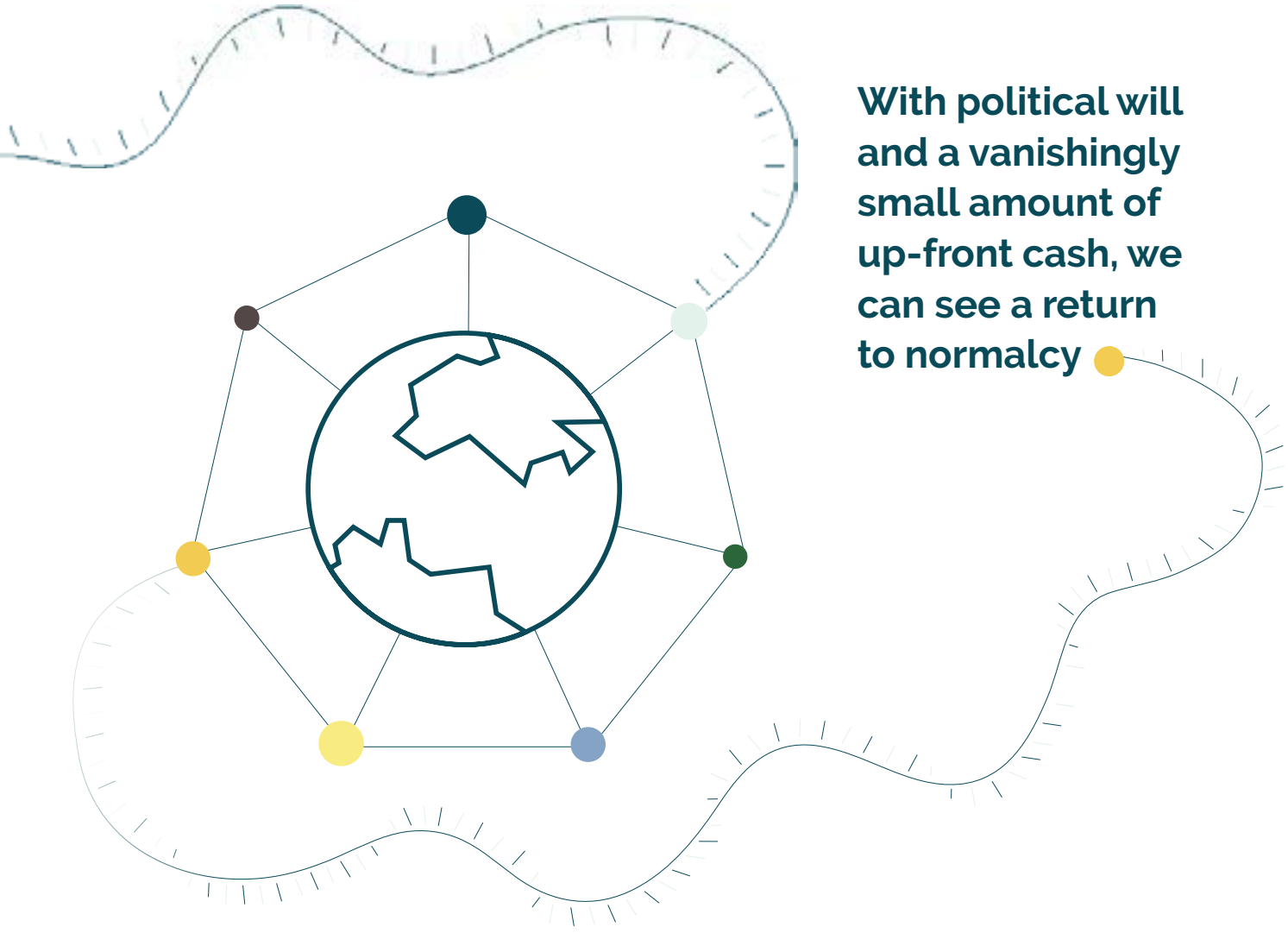
# CONCLUSION

The last year has been a showcase for the power of science and of human ingenuity. To go from discovering a new virus to getting a vaccine for that virus into millions of arms within a year is extraordinary, when the normal process takes a decade or more.

But we are not competing against our own expectations – we are competing against the virus. Even this astonishing, unprecedented effort might not be enough, if we do not vaccinate enough people fast enough to suppress the pandemic.

Luckily, there are simple things that we can do. Building the seven factories we envisage could scale up production enough to dramatically change the speed of rollout; and the cost of each would be negligible, compared to the cost of the pandemic itself. Improving vaccine technologies and supply chains would make it easier to get into people's arms in developing nations much faster.

None of this is insurmountable or even especially technologically challenging, and mRNA vaccine technology is ideally suited for the task.



**With political will and a vanishingly small amount of up-front cash, we can see a return to normalcy**

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